A STUDY OF HIGH SERUM CALCIUM LEVEL IN DIABETES MELLITUS AND ITS ASSOCIATION WITH LEFT VENTRICULAR REMODELLING

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"A Study of high serum calcium level in diabetes mellitus and its association with left ventricular remodelling"** is a bonafide work done by **Dr. M. PRAVEEN KUMAR,** Post Graduate student in the Department of General Medicine, Kilpauk Medical College, Chennai-10,under our guidance and supervision in partial fulfillment of the rules and regulations of **The Tamilnadu Dr. M.G.R. Medical University** for the award of **M.D. Degree Branch I (General Medicine)** during the Academic period from **2016 to 2019.**

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ACKNOWLEDGEMENT FROM THE GUIDE

This dissertation work done by **Dr. M. PRAVEEN KUMAR,** titled **"A Study of high serum calcium level in diabetes mellitus and its association with left ventricular remodelling"** was under my supervision for the entire duration of the study and I ensure that the candidate followed the rules of the ethical committee.

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DECLARATION

I, solemnly declare that the dissertation entitled **"A Study of high serum calcium level in diabetes mellitus and its association with left ventricular remodelling"** is done by me at Kilpauk Medical College, Chennai – 10 during the academic year of 2016 to 2019 under the guidance and supervision of **Prof. Dr. A.SAMUEL DINESH, M.D.**, to be submitted to **The Tamilnadu Dr. M.G.R. Medical University** towards the partial fulfilment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE BRANCH – I.**

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ABBREVIATIONS

Ca^{2+}	:	Calcium Ions
DM	:	Diabetes mellitus
LVH	:	Left Ventricular Hypertrophy
EF	:	Ejection fraction
FFA	:	Free fatty acids
IVS	:	Inter ventricular septum
RWT	:	Relative Wall Thickness
LVEDD	:	Left Ventricular End Diastolic Dimension
LV	:	Left ventricle
MODY	:	Maturity onset diabetes in young
MMP	:	Matrix metalloproteinases
ROS	:	Reactive Oxygen Species
PW	:	Posterior wall
RAS	:	Renin angiotensin system
SR	:	Sarcoplasmic reticulum

CONTENTS

<u>Introduction</u>

Introduction

In older days communicable diseases threatens the people invariably. Most of the people died because of unknown diseases which easily spreads to others. After the invention of penicillin the whole world came out from the communicable disasters. After the invention of many vaccines, a lot of communicable diseases are eliminated from the world. Because of modernization and globalization the physical activity of the people is almost reduced. And because of hybridization and adulteration patient food habits also changed drastically. Apart from this the environmental changes like air, water and land pollution makes the world unfit for healthy survival. The scientific success of this era is changing of the world from communicable disease to non communicable disease.

In this growing world many people are dying because of non communicable disease complications. In this century the most controllable and dreadful non communicable disease is diabetes mellitus. Day by day the number of diabetic patient is increasing. As per new survey 425 million people are affected by diabetes throughout the world. India's diabetes population is 74 million on 2017. But it will touch 134.3 million by 2045. Current expenditure of India is 31 billion dollars for diabetic health care management.

Diabetes is not the simple term like elevated blood sugar level. It is the backbone of many uncorrectable medical conditions. Every organ of our human body including kidney, brain, heart, eyes are directly affected by diabetes and many organs are indirectly affected by diabetes in the term of poor healing, increased infection and drug resistance. To prevent those complications keeping the diabetes in a controlled state is very important.

Apart from the organs, diabetes alters the metabolic components of the body. It produces the metabolic abnormality in both extreme like hypocalcemia as well as hypercalcemia, hyponatremia and hypernatremia. Because of this metabolic abnormalities many internal structures which depends the metabolic products are also affected. Internal organelle dysfunction finally leads the organ dysfunction and death.

Hypocalcemia is one of the important complication of diabetes mellitus. It occurs when the patient develops renal insufficiency. But hypercalcemia occurs in diabetes due to many mechanisms including insulin resistance. Meanwhile hypercalcemia itself produces insulin resistance. And the calcium is the important one for the production of insulin and glucose uptake in the cells.

Ionized serum calcium is the active form of calcium. Around 40% of calcium is protein bounded. Before commenting about the calcium level, serum albumin should be considered. Because low serum albumin level have a effect on serum calcium. To avoid this things this study is conducted to evaluate the cardiac complication of calcium by excluding the conditions which produces hypoalbuminemia. By using the serum calcium (spot) we can able to identify the cardiac complications.

Heart is the vital organ of our body. Any changes in the function of myocardium will affects the function of whole body system. Heart is damaged by many conditions like hypertension, diabetes, dyslipedemia and also hypercalcemia. Eventhough the hypercalcemia is not defined as risk factor for cardiac complication in older days, many trials and studies are proved that hypercalcemia will produce severe cardiac abnormality including systolic and diastolic dysfunction.

In 1982 Hockman and Buckey was coined the term “remodeling”. Remodeling is based on morphological changes of the heart. The morphological changes include ventricular cavity diameter, wall thickness, scarred area. So the remodeling is defined as it is the morphological changes of the heart after injury. Myocardial ischemia is the important disease which produces ventricular remodeling and cardiac dysfunction. Apart from MI many cardiac conditions are benign and some are significant. But some benign condition will progresses into significant myocardial abnormality. cardiac muscle hypertrophy will occur in many subjects like athelets, pregnant women. But that does not produce any significant damage. But a middle aged man or women develops the same hypertrophy because of hypertension or diabetes or hypercalcemia which in turn leads to hypertrophic changes finally leading to cardiac failure, arrhythmias and death. Cardiac hypertrophy will develops in many forms like concentric or eccentric. Hypertension and aortic stenosis produces concentric hypertrophy that is called as pressure overload. Chronic mitral or regurgitation will produces eccentric hypertrophy that is known as volume overload. Hypercalcemia produces both pressure and volume overload. This changes finally progresses into ventricular dysfunction and death.

This hypertrophic changes can be easily detected by echocardiography. We can also predicts the left ventricular remodelling by assessing serum calcium level in diabetic patients which can be used to save the patient from cardiac failure. And many newer drugs are also identified to prevent the left ventricular remodeling.

Hypercalcemia can cause left ventricular remodeling by producing vascular calcification and increases the calcineurin pathway. Apart from this way hypercalcemia also induces cardiac remodeling by altering the lipid metabolism. Hypercalcemia itself produces dyslipidemic effect by inhibiting the lipid catabolism in initial steps. Alteration in the cytosolic calcium levels determines the ventricular systolic and diastolic dysfunction.

Generally 8.5- 10.2 mg/dl is considered as normal serum calcium as per standard text books. Symptoms of hypercalcemia will develops if serum calcium increases more than 12. So the level 10.2 to 12 is the asymptomatic hypercalcemic level. This study is designed to identify the association of elevated serum calcium with left ventricular remodeling in diabetic patients.

AIM OF THE STUDY

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Assess left ventricular dimension and wall thickness mass in diabetic patients having high serum calcium level.

OBJECTIVES:

- Determination of left ventricular dimension in diabetic patients having high serum calcium
- Effect of serum calcium on left ventricular remodeling through cholesterol profile alteration.

REVIEW OF

LITERATURE

REVIEW OF LITERATURE

Diabetes mellitus:

Diabetes is called as Metabolic cum vascular disorder because it is due to altered metabolism of carbohydrate, protein, fats and these alteration will finally causes organ dysfunction. Organ dysfunction is due to Microvascular complication of diabetes. This Microvascular complication leads to permanent damage in kidney, heart, eyes and nerves. This effects in diabetes is due to either insulin deficiency or insulin resistance.

Types of diabetes mellitus:

Type 1 diabetes mellitus – beta cell destruction diabetes:

Insulin dependant diabetes mellitus term is now obsolete. Rather than that term now it is called insulin deficient diabetes mellitus. Major mechanism of this type is pancreatic beta cell destruction. This destruction is due to either autoimmune cause or idiopathic cause. Main auto antibodies are islet cell antibodies and glutamic acid decarboxylase (GAD) antibodies. In idiopathic variety there wil be no auto antibodies but this variety is associated with other auto immune disorders like autoimmune addisons, auto immune thyroiditis, ovarian failure, vitiligo and poly glandular autoimmune disorder. This type 1 diabetes will occurs mainly children and adolescents. The slow onset type of type 1 DM is also called as late onset autoimmune diabetes of adults (LADA). Hyperglycemia, coma, ketosis due to sudden withdrawal of insulin is more common in type 1 diabetes mellitus.

Type 2 diabetes mellitus – resistant or secretory defect diabetes:

Mechanism of type 2 diabetes is receptor or post receptor level insulin resistance. And it is also due to increased hepatic glucose production. s. In type 2 diabetes insulin and C peptide level will be normal to high. compared with type 1, coma, ketosis are rare in type 2 diabetes mellitus.

MODY :

Early onset of type 2 diabetes mellitus is called MODY (maturity onset diabetes of the young). It will occur before 25 years of age. In MODY there is strong family history upto three or more generations. But the MODY patients does not have any auto antibodies. It is autosomal dominant pattern there are 6 types of MODY is present.

MODY type 1- hepatocyte nuclear factor 4 alpha (HNF 4 α)

MODY type 2 – Glucokinase defect

MODY type 3- hepatocyte nuclear factor 1 alpha (HNF 1 α)

MODY type 4- insulin promoter factor-1 (IPF-1)

MODY type 5- hepatocyte nuclear factor 1 beta (HNF 1 β)

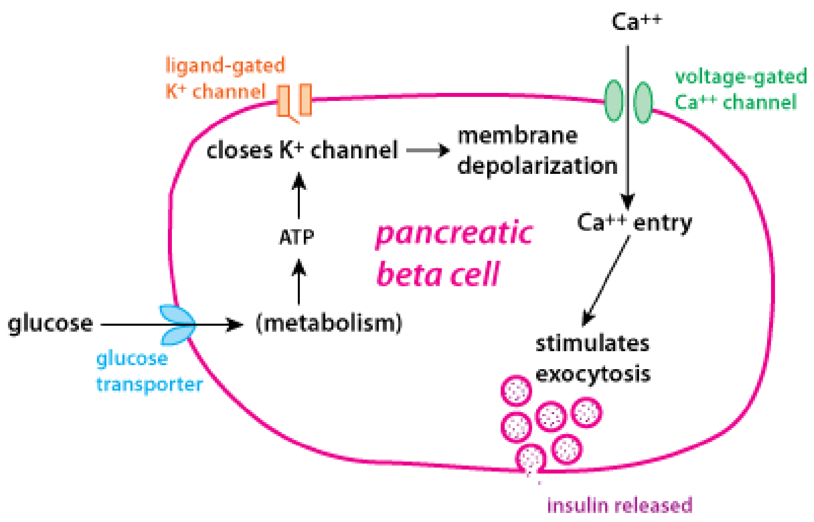
MODY type 6- nuclear differentiation factor

Gestational diabetes mellitus:

This is special variety of glucose intolerance developed during pregnancy.

Other than these some endocrine disease like cushing syndrome, auto immune addisons and hypothyroidism also causes hyperglycemia. Drugs like glucocorticoides, ACTH, thiazides, pentamidine and phenytoin also causes hyperglycemia. Sometimes malnutrition related diabetes mellitus will also occurs due to fibro calculous pancreas and protein deficiency. The main clinical features of fibro calculous pancreopathy is hyperglycemia, abdominal pain which occurs repeatedly and pancreatic calculus. About 2-4 % patients of down syndrome and turner syndrome will develops diabetes.

Mechanism of endogenous insulin secretion and role of calcium:



Carbohydrates, proteins, fat, hormonal factors and neural factors all plays a key role in insulin release. Glucose is the major determinant of insulin release. GLUT 4 receptors transports the glucose into the beta cells of pancreas. Glucose dependant insulin release is usually biphasic manner.(1) Acute insulin release is the first phase which lasts for initial 5-10 minutes. Second phase of prolonged phase persists till high glucose levels become decreased. If glucose level is less than 90 mg/dl that will affect the insulin release. In resting state ATP modulated potassium channels will kept open and voltage gated calcium channels is closed. When glucose enters into beta cell it causes depolarization of the cell membrane that closes potassium channels and opens voltage gated calcium channels. This leads to calcium influx into the cells and releases insulin. This process called exocytosis.

Apart from glucose other enzymes like glucagon and somatostatin release insulin by paracrine action. this gut hormones increases the insulin release following meal instead of parentral administration. This effect is called incretin effect. Hypothalamo-enter-insulin axis by vagal nerve also stimulates insulin release which effect is called neural effect. In type 2 diabetes mellitus insulin resistance is due to two effects. 1.normal response will occurs after supra normal levels of insulin 2. Massive doses of insulin also not able to bring the sugar values into normal. Those effects are called decreased sensitivity and decreased responsiveness respectively.

Diabetes and cardiac complication:

Uncontrolled diabetes produces adverse effects on cardiovascular system like coronary artery disease, cardio myopathy, cardiac failure and cardiac autonomic neuropathy.

Cardiomyopathy:

In diabetic patients function alteration of myocardium and cavity dilatation will occur. Diffuse ischemia is the major mechanism for diabetic cardiomyopathy. In diabetic cardiomyopathy atherosclerotic changes will occurs in intramural arteries but in myocardial infarction cases the atherosclerotic occlusion will occurs in extramural vessels. Histologically increased accumulation connective tissue in the myocardium which the intramural small vessels. The saccular aneurysms will occurs in myocardium in a localized manner. In diabetes morphological analysis shows increased glycoprotein material in myocardium with less compliant ventricular wall. Addition to that increased production of type 1 pro collagen by tunica media will also be responsible for diabetic cardiomyopathy. In diabetes reduced calcium uptake and decreased will also be responsible for cardiomyopathy.

Glucose works as fuel for myocardial contraction also. In diabetes ineffective or insufficient action on insulin leads to increased formation of extra cellular sorbitol and fructose. These osmotically active substances prevents oxygen supply to myocardium that leads to cardiomyopathy. In initial stages of diabetic cardiomyopathy only non specific ST T changes will occurs. Later stages echocardiography examination shows increased wall thickness. The increased ratio of pre ejection period/left ventricular ejection time attributes to in coordinated myocardial contraction. Abnormalities of left ventricular relaxation also occurs in diabetes patients. The peak rate of LV filling and wall thickening by M mode echo is also gives about clue of diabetic cardiomyopathy. Evaluation of diastolic dysfunction is strong predictor of cardiovascular disease in diabetic patients. Coronary atherosclerosis due to diabetes leads to myocardial scarring, fibrosis and reduced ventricular distensibility. The thickness of ventricular septum correlates with ambient insulin concentration. In diabetes high incidence of heart failure and mortality is explained by an underlying diabetic cardiomypathy. This will be exaggerated by systemic hypertension and previous ischemic heart diseases. Autonomic damage to the myocardium is responsible for painless myocardial infarction. In diabetes cardiac autonomic neuropathy parasympathetic function shows abnormalities earlier compared to sympathetic system.

Calcium:

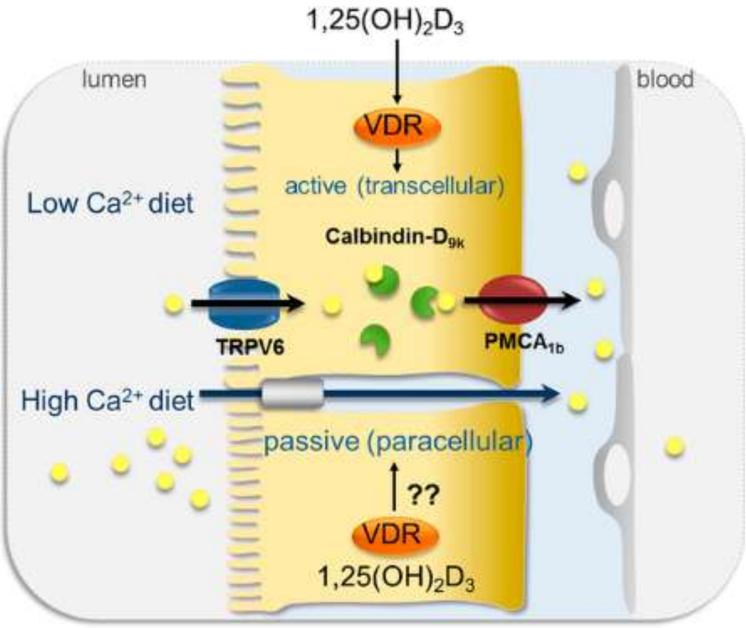
Calcium is an important mineral element of our body. 1.5-2 per cent of the bodyweight of an adult human is made up of calcium mineral. Normally an average adult human body contains around 1200g of calcium. Of these 98% of calcium is found in the bones. Around **30** g of calcium is required for developing fetus. In human body calcium is available in many forms. 40 % are plasma protein bound that are not filterable by kidney. 60 % are ultra filterable form that are excreted by kidney. In that ultra filterable form 10% are bound with phosphates, carbonates and sulphates. 50 % are in free form. This free form calcium called as ionized calcium. This ionized calcium is metabolically active form.

Functions:

Plasma ionized calcium modulates many vital functions including formation of bones and teeth, cardiac function, contraction of skeletal muscles, coagulation of blood and, milk production. And it also important for the transmission of electrical and chemical messages that arrive at a cell membrane and keeps the cell membrane intact. Calcium is useful for the metabolism of enzymes and many hormones. In the retina, it transforms the light energy to electrical impulse. As a whole, calcium ion controls many vital functions ranging from muscle contraction to cell division and cell death.

Absorption:

Milk, egg, fish are high calcium rich and readily available calcium sources. The green leafy vegetables, cereals and millets are cheapest dietary sources of calcium. calcium is highly present in ragi. Rice is a poor source of calcium. Normally about 20-**30** percent of dietary calcium is absorbed in human body. Absorption of calcium is decresed by the presence of phytates, oxalates, and fatty acids in the diet and absorption enhaced by vitamin D.



Calcium homeostasis:

Three organs of our body maintain calcium homeostasis are bone, GI system and kidney. Calcium is absorbed in GI tract. 99 % calcium deposited in bones along with phosphates. Fine tuning of handling of calcium is modulated by nephrons. In healthy states excessive calcium is eliminated by kidney. And in deficient states kidneys reabsorbs calcium. Three hormones regulates calcium homeostasis.

1. parathormone from chief cells of parathyroid gland
2. active form of vitamin D secreted by proximal tubular convoluted tubules
3. calcitonin from para follicular cells of thyroid gland.

Parathormone:

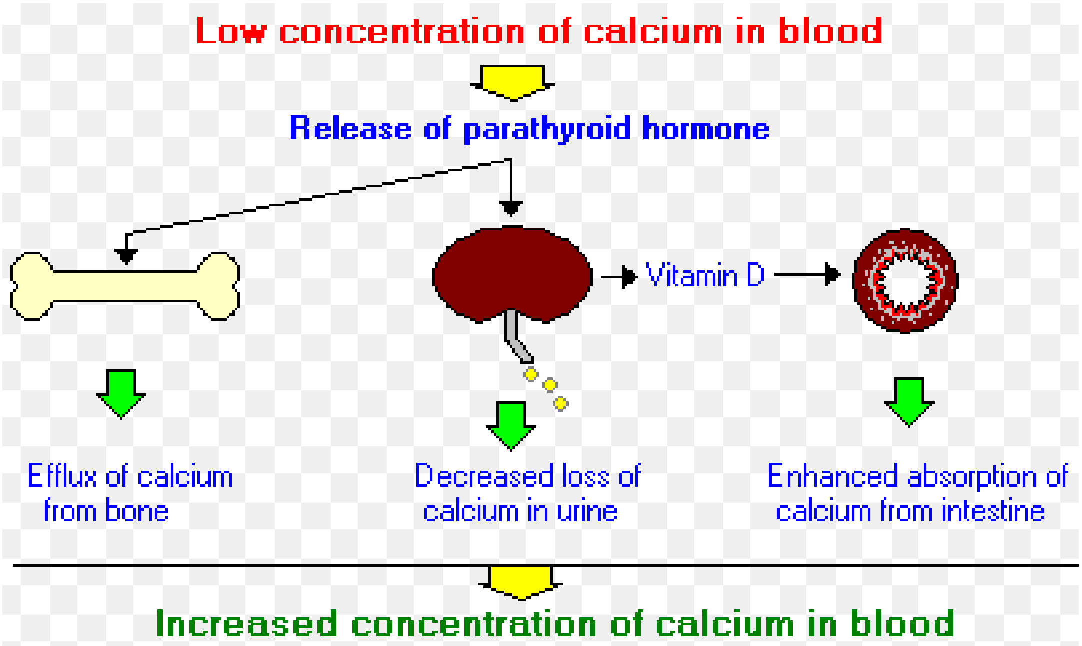
Diminished free calcium is the important stimulator of parathormone. Calcium receptors are present in the surface of the chief cells. These receptors are G protein coupled receptor. In acute calcium deficient states the ionized calcium stimulates the granules in which parathormone are stored. In chronic calcium deficient state the ionized calcium not only stimulates the granules but also nucleus which tends to produce more parathormone. Parathormone released in a state of pre pro parathormone. Then it cleaves and forms parathormone.

There are two types osteal cells. Osteoblasts and osteoclasts. Osteoblasts produces bone mineralization and osteoclasts causes demineralization. In body type 1 collagen is present in bone. It gives tensile strength to the bone.

If serum calcium level is reduced in systemic circulation it activates parathormone hormone. Parathormone receptor present in osteoblasts not in osteoclasts. Parathormone enters in osteoblast cells by G protein coupled receptor and produces more amount of adenyl cyclase and cyclic AMP. This cyclic AMP produces protein kinase A which activates the nucleus of osteoblasts and produces some proteins. those proteins are attaches into osteoclasts and activates it. In bone calcium is bound with phosphate makes hydroxyappetite complex which gives strength to bone. This calcium, phosphate, collagen forms bone mineralization. Osteoclasts attaches to the collagen with integrins. After that it will secretes proteolytic enzymes will cleaves bony part into calcium, phosphate and collagen (hydroxyprolene). This released hydroxyprolene is excreted into urine. Elevated hydroxyprolene in the blood is the marker of bone destruction. Alkaline phosphatase is the marker of bone formation.

These released calcium and phosphate enters the kidney and freely filtered by glomerular capillaries. Parathormone role is kidney is to reabsors calcium and secretes phosphates. Normally in proximal convoluted tubules special transport is situated is called sodium- phosphate co transporter. This transporter transports phosphates from glomerular tubule to interstitium. Paratharmone works on this place to prevent this reabsorption. Parathormone G protein coupled receptors stimulated and activates adenylcyclase that will produce increased cyclic AMP. This increased cyclic AMP produces protein kinase A that will lead to phosphorylation and inhibits the sodium-phosphate co-transporter pump. So phosphate will not reabsorbed and excreted through urine.

Calcium is not reabsorbed in proximal convoluted tubule. So it enters into distal convoluted tubule. In distal convoluted tubule there is two pumps are present to reabsorb calcium ions. One is calcium ATPase pump another pump is sodium – calcium exchange pump. Parathormone G protein coupled receptors also present on distal convoluted tubule. Paratharmone stimulates and activates adenylcyclase that will causes increased cyclic AMP production . This increased cyclic AMP produces protein kinase A which enhances the action of both the pumps. By this calcium is actively reabsorbed and enters into systemic circulation but phosphate will not. Thus parathormone normally causes hypophasphatemia and hyperphosphaturia and hypercalcemia.



<u>Role of vitamin D</u>:

Normally in skin cholesterol is stored in the form of 7 dehydrochlolesterol. After sunlight this 7dehydrochlolesterol is converted into cholecalciferol. This cholecalciferol is inactive form. Then it is transported into systemic circulation and reaches liver. Liver produces hydroxylation in 25th position of cholecalciferol and produces 25 hydroxy cholecalciferol. This form is also an inactive. Finally it reaches the kidney. In kidney another hydroxylation occurs at 1 st position and makes the compound into 1,25 dihydroxy cholecalciferol, which it is the active form. Vitamin D increases both serum calcium and serum phosphate level. Normally serum calcium is absorbed in GI system. This absorption is controlled by a protein called calbindin. In hypocalcemic states paratharmone also activates vitamin D. this vitamin D enters in

Gl system and binds with vitamin D receptor translocates into nucleus and produces mRNA which produces more and more amount of calbindin protein. This elevated calbindin protein absorbs more and more calcium and raises the serum calcium level. Vitamin D also increases the reabsorption of phosphates from GI system. So the net effect of vitamin is hypercalcemia and hyperphosphatemia.

Calcium and diabetes:

Ca2+ ions modulates the secretion of insulin to elevated blood sugars. Calcium alters diabetes regulation by acting on GLUT 4 receptors. Insulin is normally stored in secretory granules which is present in the pancreatic beta cells. The release of insulin is mainly depends on the influx of calcium ions through voltage-gated calcium channels which is present in the beta cell membrane of pancreas. Because of insulin plays s key role in blood glucose regulation a small change in the calcium influx into the cells, alterations in the calcium flux has adverse events on beta cell secretory function and increase the risk of development of diabetes.(2) Increased cytosolic calcium concentrations in L6 myotubules leads to activation of GLUT4 transporter expression and an increase in insulin-stimulated glucose transport activity. calcium regulates GLUT4 transporter expression in a time- and dose dependent manner which occurs in C2C12 myotubules.(3) AMPK-induced GLUT4 expression is blocked by elevated cytosolic calcium in chronic conditions. And also increase in intracellular calcium levels decreases the effect of insulin in adipocytes. This effect is due to the reduced decreased receptor activity and also decreased number of GLUT 4 receptors. Obviously increased calcium levels decrease the expression of GLUT4 transporters and it leads to decrease glucose uptake and finally it produces elevated blood sugars in serum. Incidence of diabetes mellitus in primary hyperparathyroidism is approximately 9%. And incidence of primary hyperparathyroidism in diabetes mellitus is around 2%. In type 1 diabetic patients, a elevated serum calcium level is a risk factor for autoimmune hyperparathyroidism which is associated with production anti calcium sensing receptor autoantibodies. In diabetic ketoacidosis conditions, severe hypovolemic condition leads to hypercalcemia. Metabolic acidosis and bone resorption leads to insulin defiency. Insulin growth factor-1 deficiency and hypophosphatemia are potential factor for hypocalcemia.

Diabetes with hypocalcemia :

Diabetes mellitus patients has increased risk of d acute renal failure because of volume depletion. In renal failure conditions phosphates will not be excreted by kidney. An calcium is also not reabsorbed by distal convoluted tubules of nephrons. Phosphates also binds with ionized calcium and removes calcium from the blood circulation. So chronic renal failure is associated with hypocalcemia, hyperphosphatemia, hypercalciuria and vitamin D also due to inefficient production of 1 alpha hydroxylase enzyme. Diabetes is also produces hypomagnesemic effect. hypomagnesemia produces causes impaired secretion of parathormone through bone and renal tubular resistance to the action of parathormone. Vitamin D deficiency and diuretics use mainly furosemide produces hypocalcemia. In diabetic patient decreased parathyroid gland responsiveness to hypocalcemia will occur. hypoalbuminemia is associated with pseudo hypocalcemia due to Ionized calcium binds to negatively charged sites on albumin. So that reduction of total serum calcium concentration occurs even though there is normal ionized calcium levels in serum.

Calcium and lipid metabolism:

Lot of mechanisms have been identified to explain the relationship between calcium, lipids, and estrogens.(4) In premenopausal women estrogens neutralize the adverse effect of serum calcium on lipid metabolism. Many trials are concluded that in estrogen deficient state calcium supplementation contribute to increase serum cholesterol by reduced hepatic clearance. In normal situations estrogens activates LDL-cholesterol receptor thereby increases cholesterol degradation in liver. But serum calcium decreases cholesterol degradation and it also stimulates lipidssynthesis in body. 7alpha hydroxylase enzyme is involved in the cholesterol metabolism. Calcium supplementation decreases the activity of that enzyme thereby increases serum cholesterol levels. Calcium also stimulates Sterol Regulatory Element- Binding Protein (SREBP)-1c expression in fatty acid synthesis. This SREBP- 1c is a transcription factor involved in de-novo synthesis of fatty acids. SREBP pathway also plays a important role in theregulation of HDL-cholesterol metabolism in our body. In men and premenopausal state Estrogens prevents cholesterol increase by neutralizing the calcium. So the postmenopause state is more critical for some reasons because many features of metabolic syndrome, including central obesity, altered lipid metabolism, insulin resistance, and systemic hypertension will occurs. These abnormalities may be due to 1. ovarian failure 2. central fat redistribution associated with estrogen deficiency.(5) Hormone replacement therapy will produce beneficial effect on lipid metabolism in postmenopausal state. Nowadays many trials proved that the combination of calcium supplementation and estrogens deficiency will affect the lipid profile that leads to cardiovascular risk. Post menopause women have the worst lipid profile that is associate with higher serum calcium level.(6)

Calcium and contraction in cardiac muscle :

Calcium is the important ion for contraction of cardiac muscle. In cardiac muscle calcium is highly stored in sarcoplasmic reticulum. This calcium is released from SR by active process. Apart from this many receptors and ion channels are present in sarcolemma that are participates in calcium regulation system. The released calcium from sarcoplasmic reticulum activates actin myosin compenent and leads to muscle contraction. This process not only depends the calcium channels and calcium transporters but also the precise locations and spatial arrangement of calcium. The depolarization occurs in neuro muscular junction. cardiac pacemaker opens L-type (longitudinal type) Calcium channels which are situated in the surface membrane. The entry of a small amount of Calcium resulting large increase of calcium in the dyadic space- the area bounded by the transverse tubule and sarcoplasmic reticulum of cardiac myocyte. Ryanodine receptors normally situated in the membrane of sarcoplasmic reticulum. The increase of calcium in dyadic space will leads to confrontational change of ryanodine receptors and calcium is released from sarcoplasmic reticulum through the ryanodine receptors. This process is also called as calcium induced calcium release.(7)

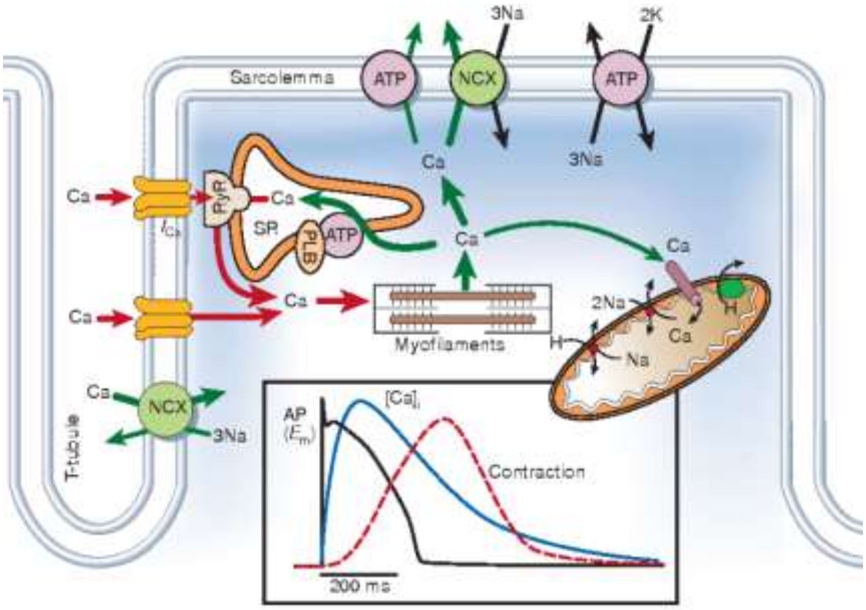


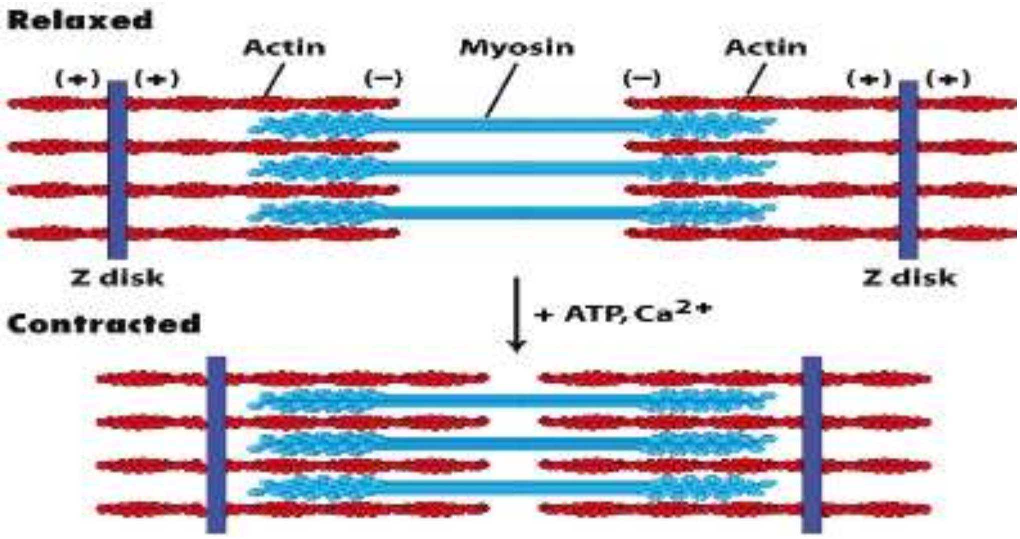
Figure showing the calcium influx and efflux during excitation contraction coupling

Transverse Tubules

Transverse tubules or T tubules are the deep invaginations of the sarcolemma. voltage-gated calcium channels are highly present in the T tubules. This T tubules are tightly coupled with ryanodine receptors of the sarcoplasmic reticulum. This forms the dyadic space with SR. dyadic space calcium change leads to calcium release from the sarcoplasmic reticulum. In heart failure conditions the ultra structure of T tubule is altered. Because of this structure alteration, the Transverse tubules become separated from the sarcolemma and leaves the ryanodine receptor orphaned that impairs calcium induced calcium release. Dyadic space calcium transits mainly depends on calcium diffusion. The altered T tubule structure leads to dys synchronous Ca2+ transits that causes poor excitation contraction coupling that is the trigger for arrhythmic activity. Junctophillin is the protein maintains the architecture of transverse tubules. Many studies concluded that disruption of junctophillin leads to cardiac hypertrophy and ventricular arrhythmias. Beta adrenergic blockers and sildenafil reduces the disruption of alteration of t tubule architecture.

The magnitude of calcium rise is not only depends ryanodine receptors and calcium in transverse tubules but also the calcium binding buffers and mitochondria. For systolic contraction calcium is needed in cytoplasm in higher level. For diastolic relaxation calcium should be low in cytosol. This can be maintained by influx-efflux mechanism. For influx of calcium ryanodine receptors plays a major role. For the efflux property two buffers are needed. They are SERCA (Sarco/endoplasmic Ca-ATPase) and sodium–calcium exchange (NCX) channel. SERCA causes calcium efflux by moving the calcium ions into the sarcoplamic reticulum. Sodium–calcium exchange (NCX) channel reduces the cytosolic calcium by pumping the calcium out of the cell. Apart from this two major mechanisms, the increased cytosolic calcium inactivates the L type calcium channels which are present in the membrane of cardiac cell. All these three events continues till the calcium influx and efflux are equal in cytosol.

The inward current from neuro transmitter signal depolarizes the cell membrane and immediately opens voltage-gated sodium channels. Because of this opening large amount of inward sodium current will occur. The inward sodium current depolarizes the cell membrane. This depolarization reaches the cell membrane potential which is permissible for opening of voltage gated calcium channels. Opening of calcium channels leads to inward flow of calcium ions. This long standing inward current is responsible for plateau phase of myocardium.



The released calcium from sarcoplasmic reticulum binds with troponin C. tropomyosin are integral component of actin. The actin binding protein is the protein which binds the tropomyosin to actin with van der wal forces. Because of this interaction myosin cannot be bind with actin. Calcium removes the tropomyosin from the actin filament and enhances the binding of myosin and Facilitates formation of cross bridges between actin and myosin that finally leads to myocardial contraction. Inward calcium current is inactivated by voltage gated calcium channels and the simultaneous opening of voltage-gated potassium channels that allows action potential repolarization, that is needed for ventricular relaxation. Ventricular relaxation mainly depends on a decrease in inward flow of calcium current that is permissible for unbinding cross-bridges. Sodium calcium exchanger exchanges 3 sodium for only one calcium it produces net positive charge.

Cardiac hypertrophy:

If the heart faces any hemodynamic stress or burden it compensates the stress by three mechanisms. The important mechanism is augmentation of cardiac muscle mass to bear extra work load. Other mechanisms are neurohormonal and excessive cross bridge formation as per frank starling mechanism. The neurohormonal mechanism is deleterious if continued prolonged time. Excessive cross bridge formation mechanism has limited in scope, and the it is also deleterious as a chronic adjustment. So the increasing cardiac muscle mass has a major role in the compensation for hemodynamic burden or overload. Cardiomyocytes are become terminally differentiated soon after birth. Because of this increased work load, hypertrophy occurs in already existing muscle. Two types of overload occurs to compensate the load. One is pressure overload and another one is volume overload. In pressure overload conditions like systemic hypertension and aortic stenosis, sarcomeres are added in parallel direction that leads to increased width of myocyte and causes ventricle wall thickness augmentation. This remodeling effect of heart is also called as concentric hypertrophy.(8)

In volume overload conditions like chronic mitral regurgitation, chronic aortic regurgitation and severe anemia addition of sarcomere in series leads to myocyte lenghthening that also increases the ventricular volume.(9) This pattern of cavity dilatation with a decrease in ratio of wall thickness is called eccentric hypertrophy. In initial stages, the eccentric hypertrophy is also compensatory mechanism to alleviate the cardiac burden. But in long term eccentric hypertrophy is sometimes deleterious because it increases the risk of ventricular arrhythmias and left ventricular failure.(10)

Pathogenesis of ventricular remodeling :

Many studies proved that a mechanical signal initiates the biological events that leads to coordinated cardiac muscle growth. So the signals for volume overload and pressure overload are different. In pressure overload myosin heavy chain synthesis increases by 38% within hours. This augmentation is mediated by an increase in translational efficiency of biological signal modulators. But in volume overload myosin heavy chain degradation rate is decreased that increases left ventricular muscle mass. Changes in radius, feedback loop, thickness, and pressure all are regulates the mechanical signal. If these factors modulates regularly and correctly hypertrophy will be typical. If large myocardial infarction occurs which imposes a eccentric hypertrophy on the remaining myocardium that leads to ventricle dilatation and increase in LV mass. Even though the initial dilatation is compensatory to maintain the ejection fraction, adverse remodeling will develops. Because of this remodeling the ventricle becomes more spherical and ventricular wall stress will become increases. In concentric hypertrophy wall stress is subnormal, and ejection fraction is normal or supernormal. Both concentric and eccentric hypertrophy are usually accompanied by gene reprogrammig complex change. The changes are the re-expression of immature fetal cardiac genes like (a) genes that modify motor unit regulation and composition (b) energy metabolism modification genes (c) hormonal pathways encoding genes (eg, ANP, ACE). The parasympathetic and sympathetic receptors are down regulating the beta 1-adrenergic receptors and M2 muscarinic receptors. Increased ratio of angiotensin II to Angiotensin 1 receptor subtypes also plays important role. (11)

The physiology of hypertrophy is an increase in the number ofsarcomeres which are force-generating units of myocyte. The mechanical input like pressure or volume is transduced into a biochemical event. This activated biochemical event by calcium calmodulin pathway causes activation calcineurin. This calcineurin modifies gene transcription factors like NFAT in the nucleus. The important transducer is focal adhesion complex and integrins that connect the internal cytoskeleton of the cell to the extracellular matrix. Multiple tyrosine-phosphorylated kinases and serine-threonine kinases like calcinuerin are implicated in the signaling pathway of hypertrophy. The disruption of cell-cell and cell-ECM contact is sufficient to modulate both cell growth (hypertrophy). In chronic hypertrophy situation changes in integrin expression and integrin shedding into adjacent extra cellular matrix raises the potential for disordered biomechanical signal transduction for suboptimal myocyte growth. In animal models acute biomechanical signal transduction is accompanied by recruitment of the G-protein–coupled neuro hormones like angiotensin II and endothelin- 1.

In clinical medicine neurohormonal signaling molecule serves as a master switch for ventricular hypertrophy. Many trials shows that via the AT1receptor, angiotensin II plays a important role in induction of hypertrophy. Angiotensin II can directly induce the molecular events of cardiac myocyte growth and it is required for the growth of stretched neonatal myocytes. After a vast search for a signaling molecule for cardiac hypertrophy recently identified molecule is calcineurin. It is a calcium calmodulin-dependent phosphatas. In transgenic mice over expression of the calcineurin signaling pathway produces hypertrophic change that will be suppressed by pharmacological agents called calcineurin inhibitors. But calcineurin inhibitors are fail to suppress hypertrophy in humans with hypertension after cardiac transplantation. Many experimental animal and human observations suggest that thousands of signaling pathways modulates cardiac hypertrophy, with the potential for recruitment of an alternate signaling pathway when any single pathway is inactivated.

<u>Hypertrophy and Connective Tissue</u>

In cardiac hypertrophy to support an increased pressure or volume overload myocytes are accompanied by increases in the surrounding structures of connective tissue and ground substances well as the capillary and nerve networks in a coordinated manner. The connective tissue is primarily made up of collagen and also less amount of elastin, fibronectin and laminin. All 4 types of collagen present in myocardium. Within that 85% of total collagen is made up of type 1 collagen in myocardium. The collagen complex provides a mechanism for translation of individual myocyte force generation into contraction of left ventricle. It prevents the development of edema, and it is responsible for the ventricular stiffness during diastole. In pressure-volume overload hypertrophy, increase collagen production that occurs to adapt the overload state. It is different from pathological collagen deposition. In pathological state collagen deposition occurs in both perivascular and interstitial area leads to fibrosis. In severe chronic hypertension and aortic stenosis patients biopsy studies shows changes in collagen architecture and severe fibrosis involving in myocardium. Sometimes it can reaches upto 30%.

<u>Role of Metalloproteinase</u>:

In volume overload hypertrophy extracellular matrix remodeling is somewhat different. In volume hypertrophy conditions the occurance of ventricular cavity dilatation is due to both myocyte elongation and changes in collagen cross-linking. collagen weave dissolution leads to increased elasticity, increased muscle fiber slippage, and an increase in ventricular chamber size. This dissolution is mainly due to activation of matrix metalloproteinase (MMPs). This MMPs is a family of zinc-containing proteins which contains collagenases, stromalysins and gelatinases. Animal models and human end-stage dilated cardiomyopathy shows that an increased metalloproteinase activation in biopsy results. Increased MMPs activation down regulation of localized tissue inhibitors is important for collagen matrix changes that allows ventricular chamber enlargement. But MMPs does not have any role in development of concentric hypertrophy.(15)

Echocardiographic Diagnosis of LVH -

Pathological hypertrophy symptoms will not manifests for longer time unless congestive cardiac failure occurs. Sometimes it leads to sudden cardiac death without any symptom. To detect that left ventricular hypertrophy non invasive echocardiographic examination is very important. 2D dimension echocardiography measures the M mode left ventricle dimension and left ventricular mass. Pathological left ventricular hypertrophy requires adjustments for sex, height, weight, and body surface are. This LV mass is calculated by a formula which includes left ventricular end diastolic dimension, inter ventricular septal thickness and posterior wall thickness. Relative wall thickness is the another factor which is calculated by 2×posterior wall thickness. By using body surface area left ventricular mass can be converted into left ventricular mass index. Relative wall thickness tells about the nature of hypertrophy.

Left ventricular mass (LVM)

Is calculated by a special formula called

Devereux formula :

LV mass (g) = 0.8 {1.04 x (LVDD + IVS + PW)^3- (LVDD)^3} + 0.6

LVEDD -left ventricular end diastolic dimension

PWTD - posterior wall thickness at end diastolic

IVSd - inter ventricular septum thickness at end diastolic

LVM index (LVMI) was calculated by correcting left ventricular mass for body surface area.

LVH is diagnosed as if LVMI > 115 in men and LVMI > 95 in women.

If relative wall thickness and left ventricular mass index is normal that LV geometry is called as normal. Increased relative wall thickness and normal left ventricular mass index called concentric remodeling. Eccentric hypertrophy is defined as increased relative wall thickness and increased left ventricular mass index.

<u>Mechanism of Diastolic Dysfunction in cardiac Hypertrophy:</u>

In LVH, abnormalities occurs in both active and phase and passive filling phase of ventricular relaxation. During myocardial relaxation cross bridge dissociation occurs after systolic contraction that is modified by pressure or volume overload.

During diastole period the rapid reduction of cytosolic calcium to basal levels occurs. Intracellular pH changes the myofilament sensitivity to calcium ions. The ATP-dependent sarcoplasmic reticulum channels moves intracellular calcium into the sarcoplasmic reticulum against a concentration gradient that leads to rapid fall of cytosolic calcium. Phospholamban is a SERCA inhibitor which is activated only dephosphorylated state. During depolarization calcium extrusion occurs in very slower phase. This activity is mainly depends on the low affinity and high-capacity sarcolemmal Sodium calcium exchanger pump. The SERCA-2 down regulation is usually ubiquitous in many trials of advanced volume and pressure overload hypertrophy. Some trails evidenced that changes in SERCA-2 levels have the potential efficacy to modify the time course of the calcium transport, cardiac relaxation. Anyway the marked reductions in SERCA-2 leads to compensated hypertrophy. And it also leads to end-stage dilated cardiomyopathy that is associated with impaired relaxation and also poor systolic performance. In dilated cardiomyopathy patients, levels of SERCA-2 are severely reduced that will be partially compensated by increased sodium calcium exchanger. Inspite of all these factors some other adaptations also occurs to modify the cross bridge attachment and myocardial relaxation phase. That adaptations are increased b-myosin ATPase activity, troponin subunit isoform expression changes, phosphorylation, and phospholamban changes. Normally myocardial relaxation properties are calculated by alternate measurements of the first derivative of LV pressure decay (2dp/dt).(16) And it also calculated by the time course of LV pressure decay between aortic valve closure and mitral valve opening. These measurements provide clues to the presence of impaired left ventricular relaxation. But it has some limitation in severe heart diseases due to those cardiac diseases has isovolumic pressure decay.

Diastolic Filling

The passive deformation properties of the myocardium, including the thickness of ventricular wall and its composition, mainly collagen deposition architecture and active ventricular relaxation influences the passive LV filling and relationship between diastolic volume and pressure. The hypertrophied cardiac myocyte has only limited role in increased ventricular stiffness. Trans mitral valve flow velocity curves explains ventricular diastolic filling and left atrial emptying which can be assessed by 2 D echocardiography technique. Radio nucleotide ventriculography is an another technique used to estimate the rates of active and passive ventricular filling. pressure gradient across the mitral valve is determined by left atrial pressure and the active fall of LV pressure to its nadir during ventricular relaxation period. This trans mitral pressure gradient is directly related to diastolic ventricular filling just after mitral valve opening.(17)

Progressive diastolic dysfunction is assessed by Doppler flow velocity curve. Three types of curves are identified during ventricular filling phase. These curves are classified by E/A ratio. Type 1- slow relaxation, type 2- pseudo normalization. Type 3- restrictive pattern. In type 1 early diastolic inflow velocity is reduced. It is associated with compensatory increase in filling due to left atrial contraction. This produces decreased E/A ratio in ECHO. In type 2 normal E/A ratio occurs. This is due to preserved ratio of the of early diastolic filling and atrial contraction. But a rapid deceleration of early mitral inflow occurs in ventricular filling phase. This is called pseudo normalization. In type 3 all ventricular filling occurs explosively in early diastole period it is associated with a very short deceleration time. This is suggestive of a high left atrial pressure because of stiff left ventricle. This type is called restrictive pattern in echocardiography. Type 3 is associated with severe left ventricular dysfunction. This is assessed by clinically as S3 gallop. It is the auscultatory marker of abrupt cessation of ventricular filling during early diastole period and increased left atrial regurgitation flow into the pulmonary circulation. This finding is also present is many volume overload states like pregnancy and exercise.

In athletes with mild hypertrophy there is no evidence of systolic contractile dysfunction. In pressure overload hypertrophy like aortic stenosis and hypertension conditions the hemodynamic hallmark is elevation the of left ventricle end diastolic pressure but a normal or relatively small left ventricular diastolic cavity volume. This decreased ventricular diastolic distensibility is related to altered passive properties that leads to high myocardial stiffness. Slowed isovolumic LV pressure decay and slowed early diastolic mitral inflow velocity and ventricular filling leads to decreased E/A ratio is described in many trials. In patients with advanced hypertrophy, this pattern may evolve into more severe abnormality of restrictive pattern of diastolic filling phase.

In many patients with aortic stenosis and aortic regurgitation states both hemodynamic and autopsy reports suggest that the prolongation of ventricular relaxation period is closely related to the severity of hypertrophy. But abnormal increases in myocardial stiffness are related to collagen architecture changes.

Ventricular relaxation phase abnormalities and passive myocardial stiffness occurs before the alterations in systolic dysfunction.

Influence of Age and Sex in Diastolic Function in LVH patients:

Concentric LVH is common in elderly patients with isolated systemic hypertension. Diastolic dysfunction like impaired relaxation has been observed in 70% of older patients with hypertension. In patients with severe aortic stenosis, sex factor greatly modulates the pattern of hypertrophic growth of cardiac muscle and diastolic function of heart. By using hemodynamic studies analysed by morphometric analysis of ventricular autopsies shows elderly patients had severe cardiac hypertrophies and interstitial fibrosis.(12) In elder population more severe impairment of ventricular relaxation, myocardial stiffness, and filling defects occurs. Left ventricular ejection fraction and mid systolic wall shortening were similar in all age groups. In aortic stenosis and similar aortic valve disease conditions men are more likely to have cavity enlargement, a lower ejection fraction, trans valvular gradient. Men compared to women has increased diastolic myocardial stiffness and more collagen architecture changes. (13)

Prognosis of cardiac Failure due to left ventricular Diastolic Dysfunction :

Not only systolic dysfunction but also diastolic dysfunction causes cardiac failure due to impaired relaxation. This impaired relaxation leads to increased left atrial pressure that will increases pulmonary capillary wedge pressure. This may present as acute heart failure. Sometimes chronic diastolic dysfunction leads to severe pulmonary hypertension that will finally leads to right heart failure that produces congestive signs and symptoms. In patients with chronic left ventricular failure associated with diastolic dysfunction with normal ejection fraction both male and female patients will develops episodic severe congestive cardiac failure and needs intensive care management.(14) Even in patients with milder degrees of ventricular hypertrophy with diastolic dysfunction, an inability to improve LV volume during exercise. Even though the heart failure patients with preserved ejection fractions had a lower mortality risk compared with patients with reduced ejection fractions heart failure patients with preserved ejection fractions had 20 % mortality rate annually. In patients with in LVH & diastolic dysfunction atrial fibrillation also have a major role. The increased reliability on atrial contraction against stiff left ventricle needs to improve the cardiac output. In patients with atrial fibrillation will make poor cardiac output and it is poorly toleratable. In pressure overload conditions hypertension is responsible for atrial fibrillation in 16% patients than other risk factors. This atrial fibrillation leads 5 to 6 fold increase of stroke risk .

Mechanism of Systolic Dysfunction:

Changes in cardiac cellular biology leads to systolic dysfunction is very complex and it is not due to a single change in gene expression. Sub endocardial ischemia due to chronic pressure overload or extreme volume overload plays important role in systolic dysfunction. This subendocardial ischemia limits exercise reserve volume and promotes myocardial fibrosis. Excessive afterload due to inadequate hypertrophy to normalize the ventricular wall stress itself suppresses systolic stroke volume independent of intrinsic changes in myocardial contractibility. This effect accounts for the drastic improvement in ejection performance after valve replacement in aortic stenosis and aortic regurgitation patients. Important mechanism for reduced myocardial contractility at the level of the myocyte is impaired calcium homeostasis. This calcium homeostasis abnormality leads to the depression of the force-frequency relationship, motor unit composition change, and relative increase in b-myosin heavy chain that occurs in both human and animals. The densification of the microtubules within the cardiac myocyte, which causes an improved internal load on sarcomere length shortening. Many assessment regarding LV midwall shortening using 2 D echocardiography allows the identification of impaired ventricular contractile function. It also useful in some patients in whom the geometric changes of concentric remodeling supports normal ejection performance. In volume overload hypertrophy myofibrils loss will occurs. Complex changes in energy metabolism due to loss of myofibrils may reduce the capacity to maintain the levels of free energy at ATP hydrolysis. This ATP is needed for optimal functioning of both the motor unit and the membrane pumps that is required for many ion homeostasis. Apoptosis may cause a repetitious low frequency loss of myocytes in the hypertrophied myocardium that would increase the biomechanical load on the remaining normal myocytes. In early stages of pressure overload conditions before the development of adaptive hypertrophy, low frequency of apoptotic cardiac myocytes are identified.

Prevalence of apoptotic myocytes are wildly variable in many studies of end-stage dilated cardiomyopathy.

Vascular calcification by calcium:

Apart from calcineurin calmodulin pathway many other biological mechanism are discovered for calcium induced cardiomyopathy. Calcium exert harmful impact on cardiovascular health by vascular calcification. Calcium phosphate deposited in cardiovascular structures in elevated serum calcium levels. Newer studies concluded that calcification of coronary arteries leads increased risk of atherosclerotic plaque that finally causes coronary ischemic. In patients with chronic renal disease, daily ingestion of Calcium supplementation has proportional correlation coronary artery disease. In addition to that calcifications, increased serum calcium leads increased blood coagulation profile and high arterial stiffness that are positively correlated with hypercoagulable state that finally leads to myocardial ischemia that eventually leads to cardiomyopathy and heart failure. This increased coagulation profile also leads to thrombus formation in many organs including brain, spleen and mesentry.

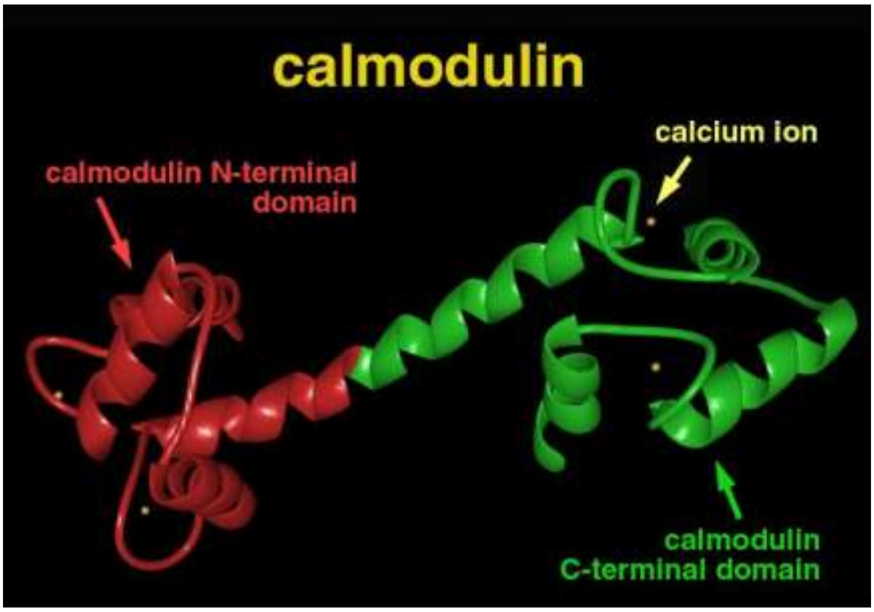
<u>Impaired calcium efflux during Diastole</u> :

To start ventricular relaxation, cytosolic calcium must be effluxed into Sarcoplasmic reticulum by SERCA or out of the cell by sodium calcium exchanger. Diastolic The sarcomere is the functional force of cardiac muscle. cardiac failure is produced by spontaneous release of calcium during diastole leads to spontaneous and highly variable diastolic sarcomere contractions that finally leads to loss of systolic function also. Calcium uptake by sarcoplasmic reticulum is reduced by reduced expression and activity of SERCA.(18) And reduced calcium uptake by sarcoplasmic reticulum due to increased inhibitory action of phospholamban. In dephosphorylated form Phospholumban inhibits SERCA activity. In phosphorylated form, the phospholumban assembles in a pentamer structure that lacks SERCA inhibitory activity. Many studies proved that phosphorylation of PLN is decreased in diastolic heart failure. Increased dephosphorylation of phospholamban is achieved by increased calcineurin activation. Some times mutation in PLN gene (R9H, R9L) leads to constant de phosphorylatation that leads to increased SERCA inhibition. The phenotypes of R9H carrier will develop dilated cardiomyopathy and premature cardiac death. Another new regulator for SERCA activity is Histidine rich calcium binding protein (HRC). HRC is low affinity at the same tie high capacity binding protein which is present in sarcoplasmic reticular lumen. It binds with triadin and inactivates ryanodine receptor. This HRC mediate a cross-talk between Sarcoplasmic reticulum calcium release and uptake. HRC is also inhibit the SERCA that is strongly associated with ventricular arrhythmias in dilated cardiomyopathy subjects due to low calcium release and prolonged efflux time.

Mitochondrial Calcium regulation :

Mitochondria consists approximately 25% to 35% of cardiac mass. Mitochondria is very essential for providing ATP to meet the energy demand of cardiac muscle function. Calcium is the important messenger for communicating cellular energy demands to mitochondria. Oxidative phosphorylation is a Calcium regulated process. Calcium increases the tricarboxylic acid dehydrogenases activity which is involved in the production of NADH/NADPH. The inner mitochondrial membrane contain aspartate/glutamate exchangers. It contains calcium binding proteins that facilitates the ATP production in response to calcium signal. Mitochondriahas a lower affinity but a higher capacity for calcium uptake. Mitochondria also contains calcium buffer which is activated according to cytosolic calcium. Excessive accumulation of mitochondrial calcium leads to mitochondrial death by increased oxidative stress and apoptotic mediators like cytochrome C. Mitochondria is the important source for pathological increases of reactive oxygen species. This ROS produces oxidative stress which damages the mitochondrial DNA and proteins that finally leads to mitochondrial dysfunction. This impaired mitochondrial bioenergetic function leads to heart failure.

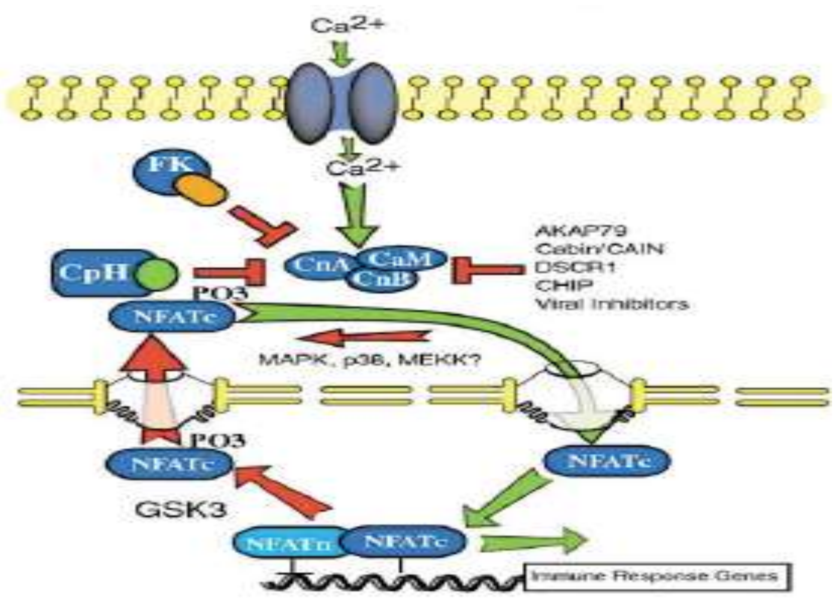
Calmodulin:



Many proteins are sensitive to serum calcium levels mainly in cellular level. The important proteins are protein C and Calmodulin. A Small dumbbell-shaped Calcium modulated protein is called as calmodulin. It is highly present in the cytoplasm of all mammalian cells. It acts as an intermediary protein that senses calcium levels and relays signals to various calcium-sensitive enzymes, ion channels and other proteins. It is composed of two globular domains which are connected together by flexible linker and those ends binds with two calcium ions. Troponin C and calmodulin are structurally similar but the difference between these two protein is length of the linker which connecting the two calcium-binding globular domains. Calmodulin’s target protein are present in different size and shapes an sequences. This calmodulin also binds with phosphatases and kinases and activates it. These enzymes are important in cell signaling, cell death and cell transport. After binding of calcium non-polar surface of calmodulin is exposed and then it binds to non-polar regions on the target proteins of the cell.

Even though calmodulin is not bound to its target proteins the connector between the two calcium binding globular domains is usually flexible. This Calmodulin typically wraps around its target with the two globular domains gripping each side. Calmodulin contains nearly four identical high-affinity calcium binding sites. The calcium-binding site is composed of a characteristic loop flanked by two alpha helix. The positively-charged calcium ion is surrounded in the loop by one glutamate and three aspartates which are negatively-charged side chains and one oxygen atom from the backbone of the protein chain

Calcineurin



It is a calcium-calmodulin dependant serine -threonine protein phosphatase. Calcineurin has two sub units

1. Calcinuerin A - 61 Kd -calmodulin binding catalytic subunit.
2. Calcineurin B – 19 Kd – calcium binding regulatory subunit

Function:

Calcineurin is activated once calcium-calmodulin complex activated. This activated calcineurin induces NFATs. In resting state NFAT will be in phosphorylated form. Calcineurin changes the NFAT from phosphorylated into dephosphorylated form and this NFAT induces DNA transcription of cell.

Because of low intracellular calcium level, very minimal amount of calcineurin is activated. If extracellular calcium rises or if there is any defect in voltage gated calcium channels it will leads to more influx of calcium from extracellular into intracellular space that leads to exaggerated activation of NFAT by calcium calmodulincalcineurin pathway. This effects will cause pathological effect. The calcineurin is useful for the biosynthesis of neurotransmitters and transport of this NT substances in synaptic terminals of brain, myocardium, skeletal muscles and kidney. Defective calcineurin pathway leads to mental retardation, down syndrome, Alzheimers disease, brain hypoxemia and cardiac hypertrophy.

In myocardium calcineurin- NFAT signal pathway is activated only when there are pathological increases in serum calcium. This pathway is not activated during pregnancy or exercise which produces physiologic hypertrophy.

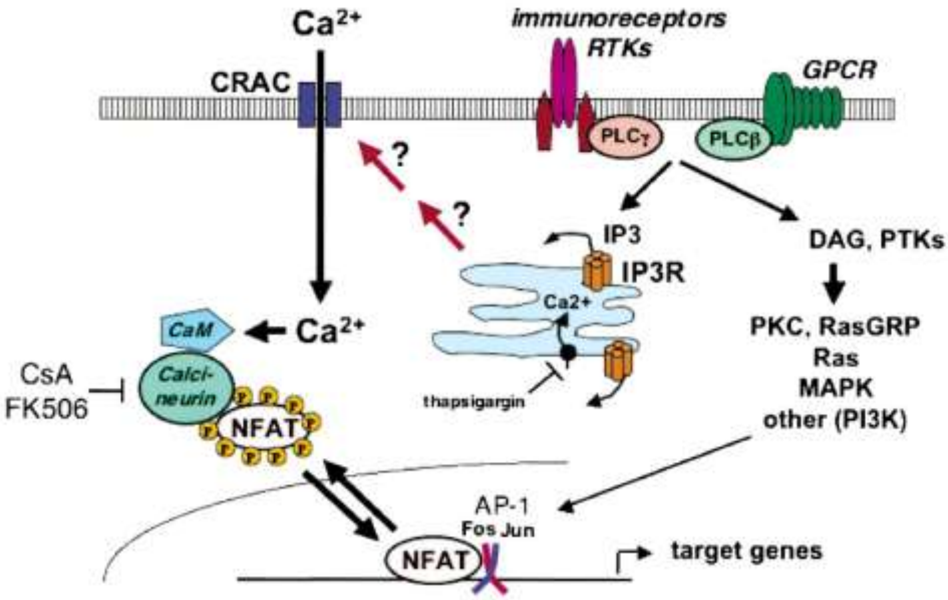
In transgenic mice calcineurin was found as a hypertrophic signaling factor based on its over expression in the heart. These transgenic mice expresses an activated mutant of calcineurin which is demonstrated a profound hypertrophic response that rapidly progresses into dilated left ventricle and leads to heart failure with in a short duration 2-4 months. Many newer trials shows that calcineurin is a sufficient inducer of the hypertrophic response. Like that many groups reported that increased cardiac calcineurin activity in hypertrophic hearts. increase in cardiac calcineurin activity leads to salt-sensitive hypertension induced cardiac hypertrophy , infrarenal aortic constriction-induced neuro endocrine-mediated hypertrophy and steroid induced cardiomyopathy .

Calcineurin inhibitors:

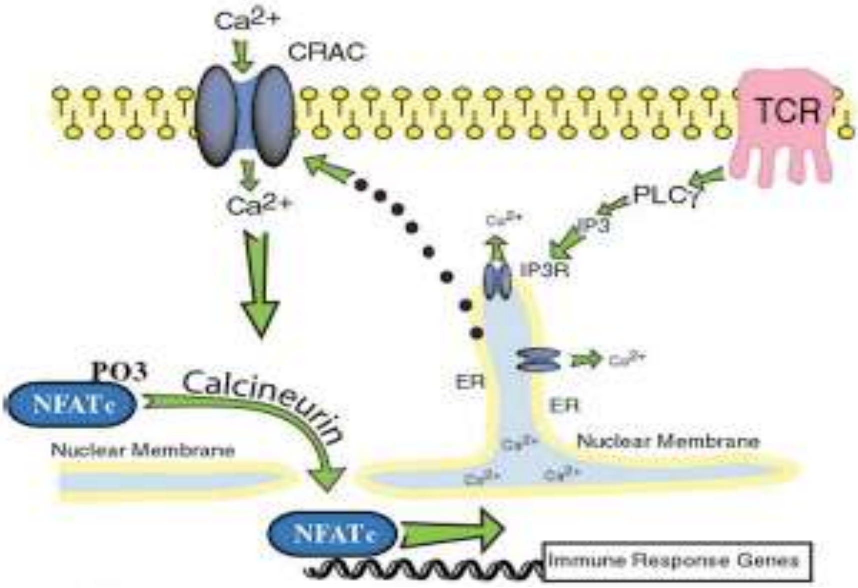
Commonly used calcineurin inhibitors are cyclosporine and tacrolimus.

Cyclophilin is an immunophillin class of protein present inside the cell. Cyclosporine enters into target cells and attaches into cyclophillin protein. This cyclosporine-cyclophillin complex finally binds with calcineurin protein and inactivates it. Even though calcium calmodulin complex overexpressed in the cells calcineurin will not to be activated. This leads to failure of transcription. Calcineurin inhibitors are commonly used for post transplant patients rheumatoid arthritis, uveitis, psoriasis, inflammatory bowel disease, bronchial asthma and dermatomyositis. It can also useful for aplastic anemia.(19)

Regulated influx of calcium release is important for the function of muscle contraction, fertilization and memory. The calcium calmodulin activated calcineurin dephosphorylates and induces the nuclear localization of NFAT transcription complexes Which is the cytosolic component. The NFAT transcription complexes assembles in the DNA and activates the cell–cell interactions genes.(20)



Normally in ligand gated receptors channel activation leads activation of phospholipase that will turns into inositol triphosphate. This inositol triphosphate is useful for the release of calcium from stored granules. This calcium is insufficient for the activation NFAT transcription complexes. So that a special calcium channel is activated. That is called calcium release activated calcium channels or CRAC channels. This signal is called inside-out signaling.



CRAC channels induced NFAT activation (inside out signal)

In embryonic state NFATc1 is present is endocardial cell which is useful for the development of valves and myocardium. During development of heart the NFATc1 receptors are restricted to epithelial-to-mescenchymal transformation cells which is finally developed into endocardial cushion. This endocardial cushion are furtherly differentiates into cardiac valves and septal walls. Many studies proved that the animal models treated with calcineurin inhibitors during embryonic state present with mal development of heart and consequently heart failure. Connexin is the protein which forms gap junctions which is useful for the transmission of IP3, influx of calcium by IP3 and CRAC channels.NFATc4 is associated with cardiac zinc finger factor GATA4. This GATA4 transcription factor is important for cardiac hypertrophy, MCIP-1 (multipotent IsL cardiovascular progenitor gene is activated once calcineurin elevation. By feedback mechanism it inhibits the further activation of calcineurin and prevents the cardiac muscle hypertrophy. Cabin/Cain, CsA or FK506 also the inhibitor proteins of calcium dependant NFAT signal pathway. These analogues will be useful to prevent cardiac hypertrophy that process is still in research.

<u>Types of NFAT:</u>

S.no	Types	Effect
1	NFATc1	Cardic morphology alteration
2	NFATc2	Immune hyperactivation Allergic response bony deformities
3	NFATc3	Hyperproliferation of lymphocytes Thymus maldevelopment
4	NFATc4	No apparent defect

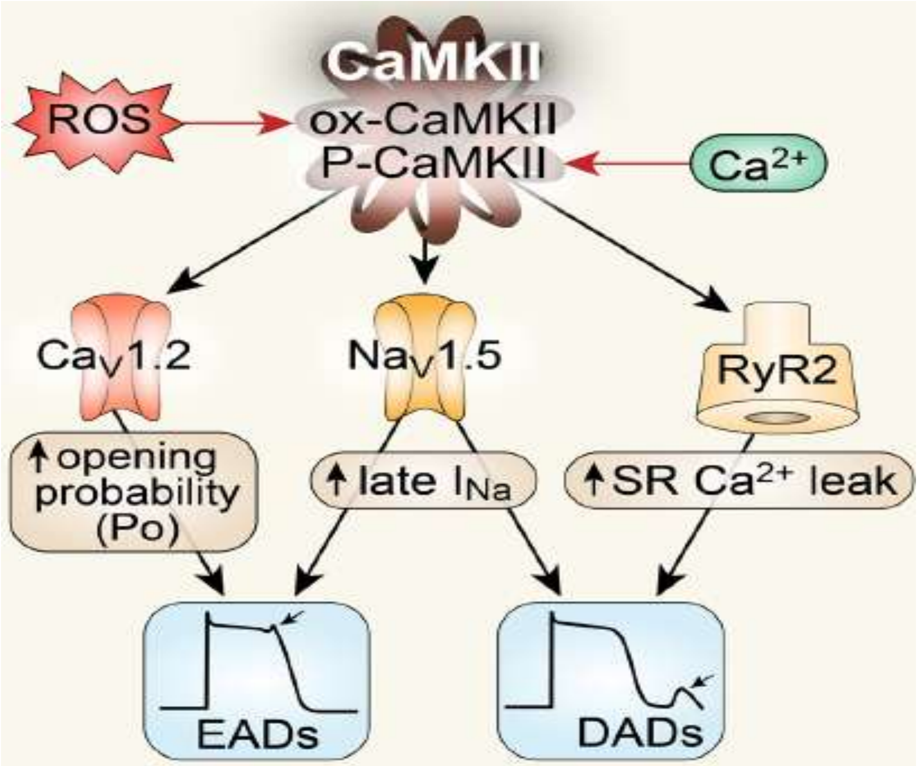
<u>Transient receptor potential (TRP) pathway and LVH</u>:

Although several Signal transduction pathways are involved in the process of cardiac hypertrophy one more important pathway is transient receptor potential (TRP) pathway. The transient receptor potential super family contains six subfamilies. They are more permeable to calcium ions into the cardiac myocyte. In TRP subfamily, especially TRPC3 is increased in cardiac hypertrophy. apart from TRPC3, TRPV2, TRPM7, and TRPP2 are also associated with cardiac fibrosis and left ventricular hypertrophy. Transient receptor potential vanilloid 3 channel has present in skin keratinocytes, dorsal root ganglion, trigeminal ganglion, spinal cord, nasal epithelia and also myocardium. TRPV3 channels activation leads to pressure overload hypertrophy of myocardium. Many studies hypothesized that the TRPV3 activation could be directly or indirectly involved in cardiac hypertrophy.

CaMKII and Arrhythmia:

Arrhythmias are more common in patient with heart failure particularly if patient ejection fraction is less than 30%. Arrhythmias leads to sudden cardiac death especially ventricular origin. Calcium hemostasis alteration leads to arrhythmias.(21& 22)

Increased oxidant stress, calcium hemostatsis alteration leads to heart failure as discussed above. In this situation calcium dependant calmodulin protein kinase II is activated.



This CaMKII makes alteration is voltage gated sodium channels, calcium channels and ryanodine receptors that will trigger arrhythmic effect. calcium dependant calmodulin protein kinase II causes phosphorylation of voltage gated calcium channels at β-subunit receptor level. That will makes increased calcium overload that consequently enhances the early after depolarization phase. Phosphorylation of ryanodine receptor by CaMKII increases diastolic SR calcium leak, that triggers the delayed after depolarization that also proarrhythmic action over the voltage gated sodium channels by CaMKII prolongs the inflow current of sodium that makes prolonged action potential finally increases EAD phase. CaMKII inhibition prevents ventricular arrhythmias in myocardial tissues which is proved in animal model.

MATERIALS AND METHODS

MATERIALS AND METHODS

This study was conducted in Government Royapettah hospital, Chennai for duration of 6 months from April 2018 to Sep 2018. A proper and complete ethical clearance was obtained from the Institutional Ethical Committee. This study was conducted after getting a informed consent from all subjects involved in this study.

- **STUDY DESIGN** : prospective cross sectional study
- **STUDY PERIOD** : six months (April 2018 to Sep 2018)
- **CONFLICT OF INTEREST** : Nil

STUDY POPULATION:

Study population consists of diabetic patients who attending medical out patient departments and admitted as inpatient in medical ward of Govt. Royapettah Hospital.

Inclusion criteria :

Patients with type 2 diabetes

Diabetes in this study will be defined by the american diabetes association as either

- Fasting plasma glucose (FBS) of >125 mg/dl or
- Post prandial blood sugars at 2 hr (PPBS) >200 mg/dl

Exclusion criteria:

- Patients with hypertension
- On treatment with sulfonylurease
- A h/o myocardial infarction, coronary artery bypass or angioplasty, atrial fibrillation, moderate to severe valvular heart disease, stroke or occlusive peripheral vascular disease, heart failure
- Serum creatinine> 110 micromoles/ L. (>1.2 mg/ d L)
- A history of parathyroid disease or vitamin D related disorder
- Medication history including vitamin D, bisphosphonate, estrogen replacement therapy and diueretics
- Uncontrolled thyroid diseases
- Patient with chronic liver diseases

SAMPLE SIZE:

by using the formula

prevalance = $4pq/E^2$

- Total number of the subjects – 206
- 95 % confidence interval
- Level of significance - $p < 0.05$
- Assuming power of study – 80%

METHODOLOGY:

After obtaining a informed written consent demographic details, past medical history and clinical examination done. Following investigation was done in all patients.

- Serum calcium
- Serum creatinine,
- total cholesterol, triglycerides,
- low density lipoprotein cholesterol (LDL-C),
- high density lipoprotein cholesterol (HDL-C)
- fasting blood glucose

- 2D ECHO – echocardiography was done in all patients. In left lateral position ECHO was performed in parasternal long axis, 4 chamber view.
- M mode was used to asses the septal wall, posterior wall thickness and left ventricular diastolic dimension.
- By using wall thickness left ventricular mass is calculated.
- Adjusting the left ventricular mass with body surface area left ventricular mass index is calculated.
- LV mass using the corrected formula

$$\text{LV mass (g)} = 0.8 \{1.04 \times (\text{LVDD} + \text{IVS} + \text{PW})^3 - (\text{LVDD})^3\} + 0.6$$

- LV mass index (LVMI): LV mass/ body surface area

RESULTS
AND ANALYSIS

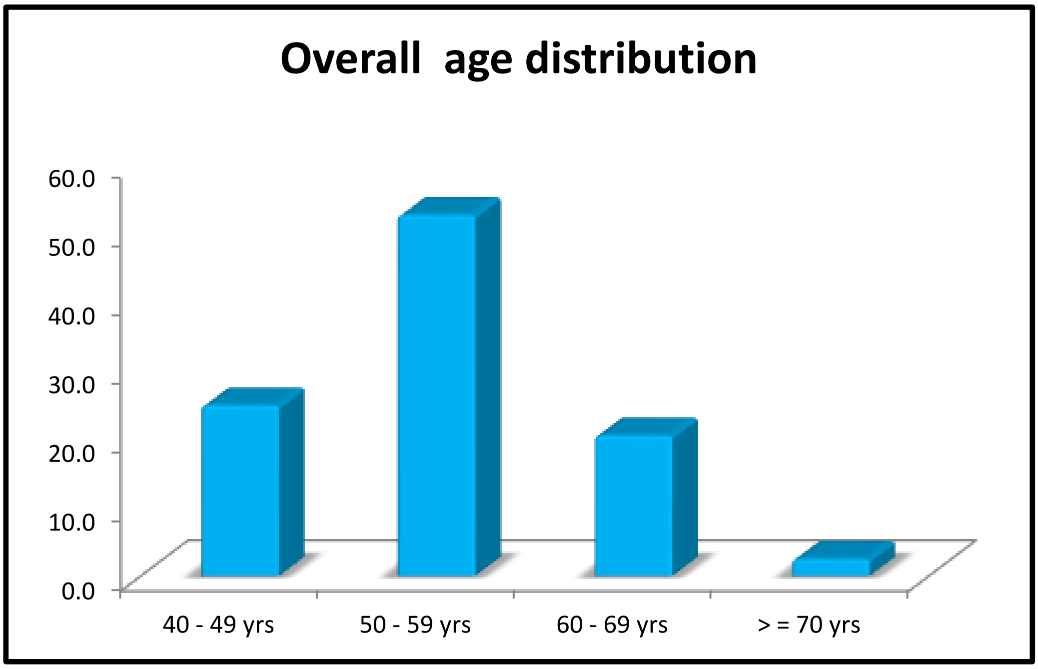
Results And Analysis

The collected data were analysed with IBM.SPSS statistics software 23.0 Version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S.D were used for continuous variables. To find the significant difference between the bivariate samples in Paired groups the Paired sample t-test was used & for Independent groups the Unpaired sample t-test was used. The identify the accuracy of the variable the Sensitivity, Specificity, PPV and NPV was used. To assess the relationship between the variables Pearson's Correlation was used. To find the significance in categorical data Chi-Square test was used similarly if the expected cell frequency is less than 5 in 2×2 tables then the Fisher's Exact was used. In all the above statistical tools the probability value .05 is considered as significant level.

<u>Overall age distribution in the study</u>

Totally 206 patients are included in this study after exclusion. All patients are diabetic patients. Most of the study subjects are with in the age limit of 50-59 years.

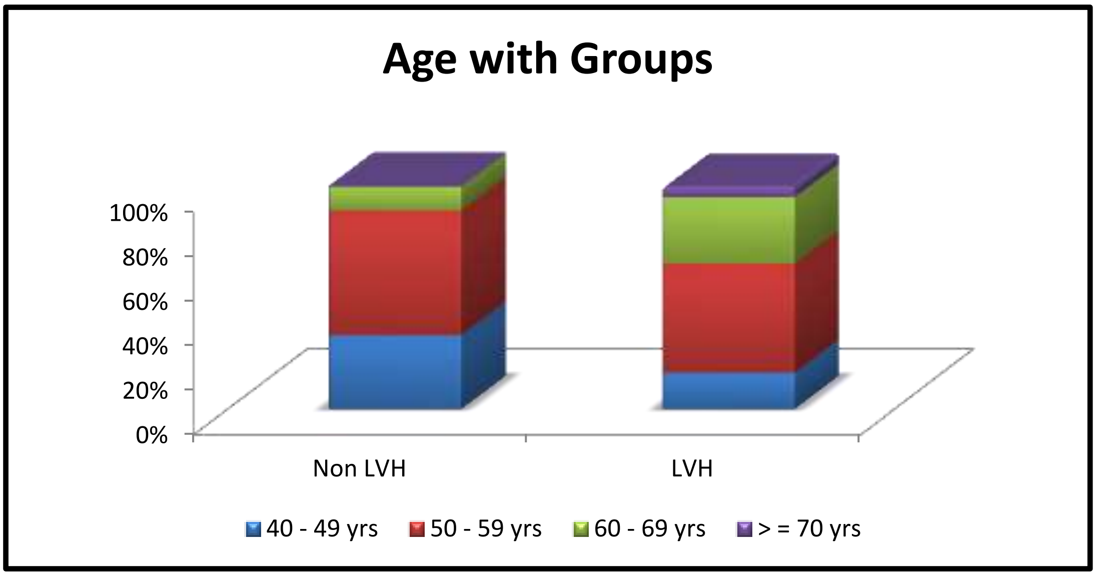
AGE	Frequency	Percent
40 - 49 yrs	51	24.8
50 - 59 yrs	108	52.4
60 - 69 yrs	42	20.4
> = 70 yrs	5	2.4
Total	206	100.0



AGE DISTRIBUTION WITHIN LVH AND NON LVH GROUP

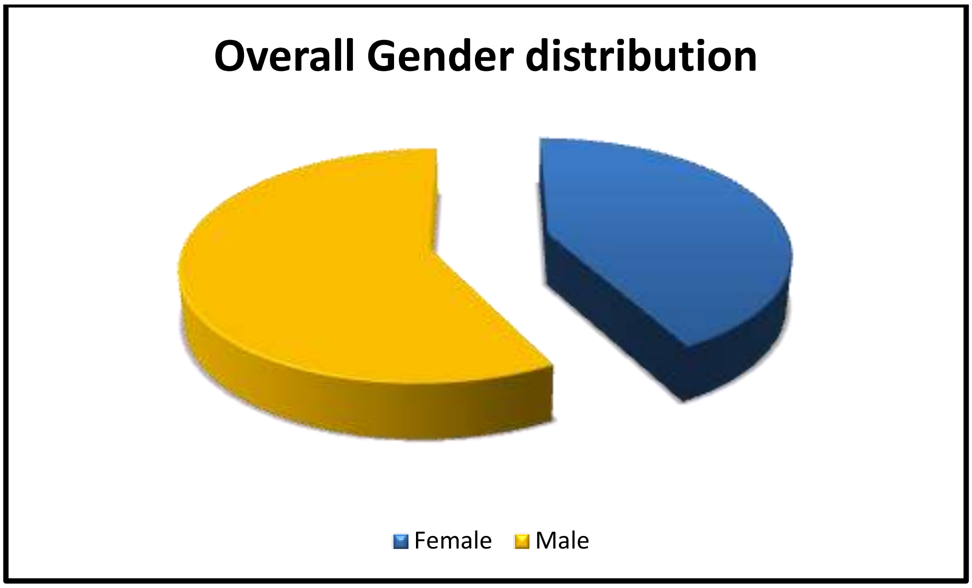
Age distribution in both LVH and non LVH group is compared. 50-59 years subjects are more in both groups compared with other age group people.

AGE			Groups		Total
			Non LVH	LVH	
	40 - 49 yrs	Count	34	17	51
		% within Groups	33.3%	16.3%	24.8%
	50 - 59 yrs	Count	57	51	108
		% within Groups	55.9%	49.0%	52.4%
	60 - 69 yrs	Count	11	31	42
		% within Groups	10.8%	29.8%	20.4%
	> = 70 yrs	Count	0	5	5
		% within Groups	0.0%	4.8%	2.4%
Total		Count	102	104	206
		% within Groups	100.0%	100.0%	100.0%

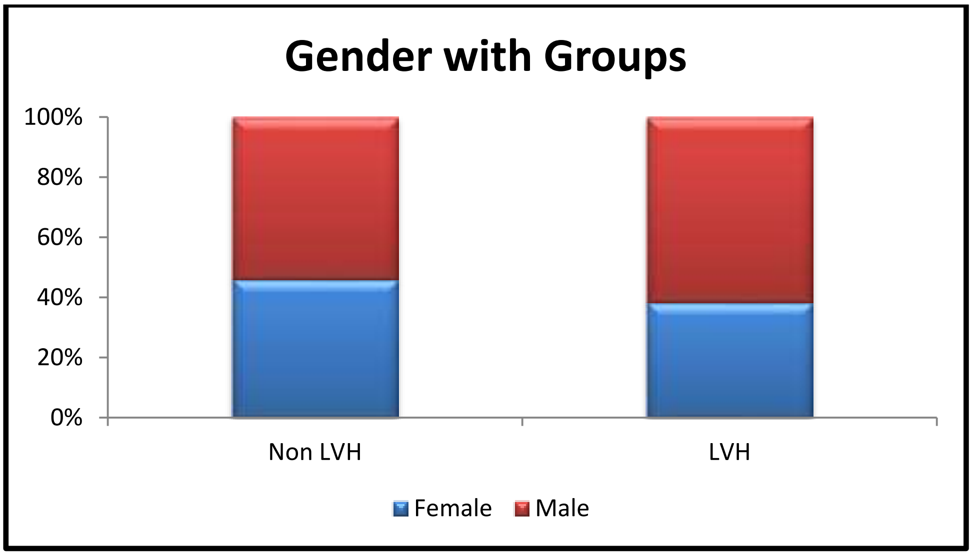


Overall Gender Distribution

Number of males are high in overall group compared with females.



<u>Gender distribution in LVH and NON LVH group</u>



Cross tabulation for gender distribution:

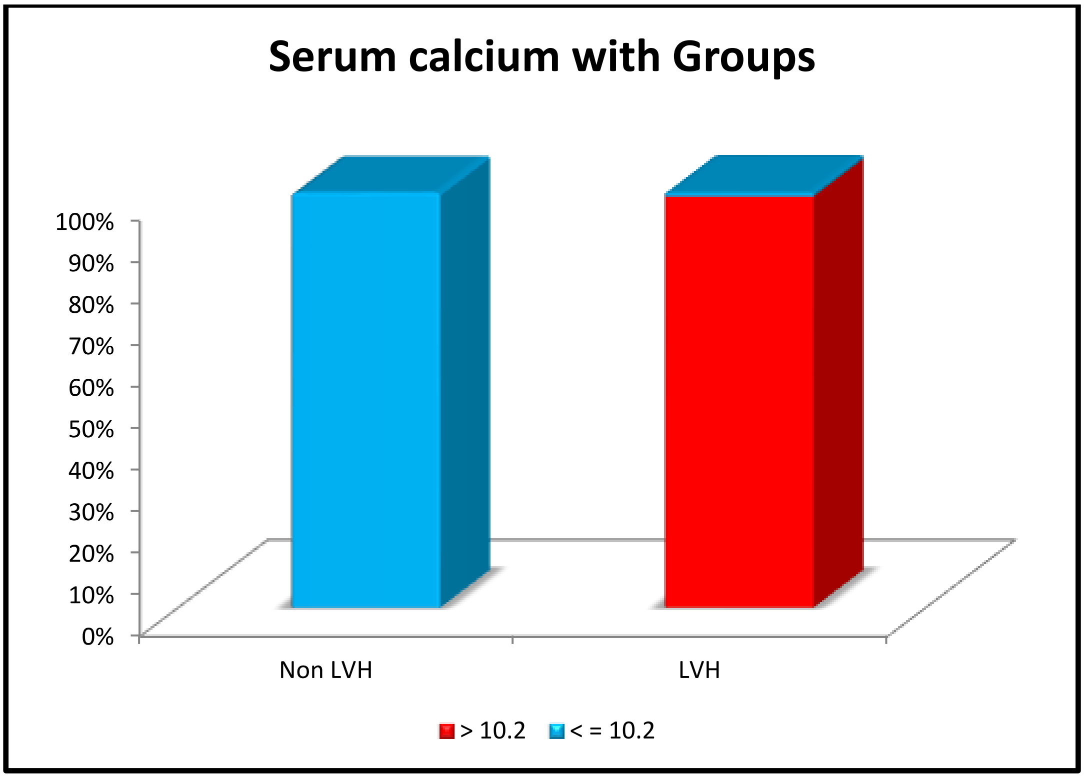
Gender		Groups		Total
		Non LVH	LVH	
F	Count	47	40	87
	% within Groups	46.1%	38.5%	42.2%
M	Count	55	64	119
	% within Groups	53.9%	61.5%	57.8%
Total	Count	102	104	206
	% within Groups	100.0%	100.0%	100.0%

By our results left ventricular remodeling occurs mostly in males compared with female irrespective of age group. But gender is not make any significant p value in LVH occurance. If at all post menopausal women will deveop LVH the occurance is very less in females compared with same age group of males**.**

<u>Serum calcium level association with LVH</u>

According to our literature serum calcium is main determinator of left ventricular remodeling by many mechanism. Serum calcium is > 10.2 in LVH group people. But in non LVH group people serum calcium level is with in normal limit that is given as < 10.2 mg/dl. 1 patient in non LVH group is having high serum calcium but does not make statistical changes in that group. The mean serum calcium of LVH group is 10.6mg/dl

Serum calcium			Groups		Total
			Non LVH	LVH	
	> 10.2	Count	0	103	103
		% within Groups	0.0%	99.0%	50.0%
	< = 10.2	Count	102	1	103
		% within Groups	100.0%	1.0%	50.0%
Total		Count	102	104	206
		% within Groups	100.0%	100.0%	100.0%

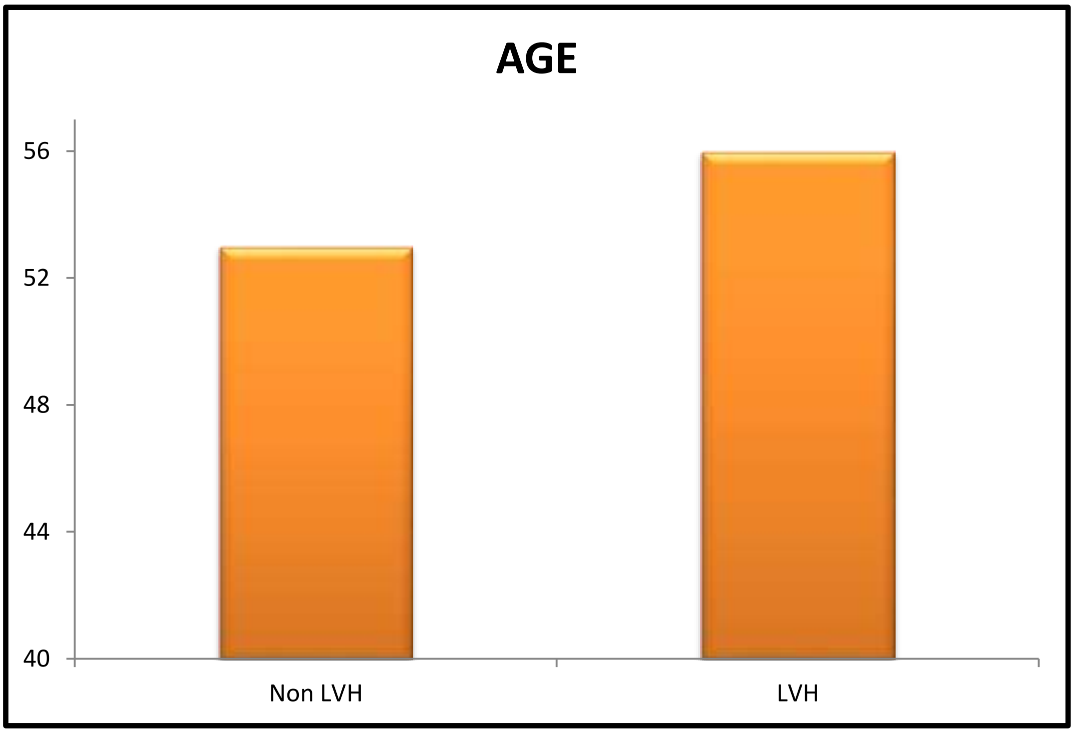


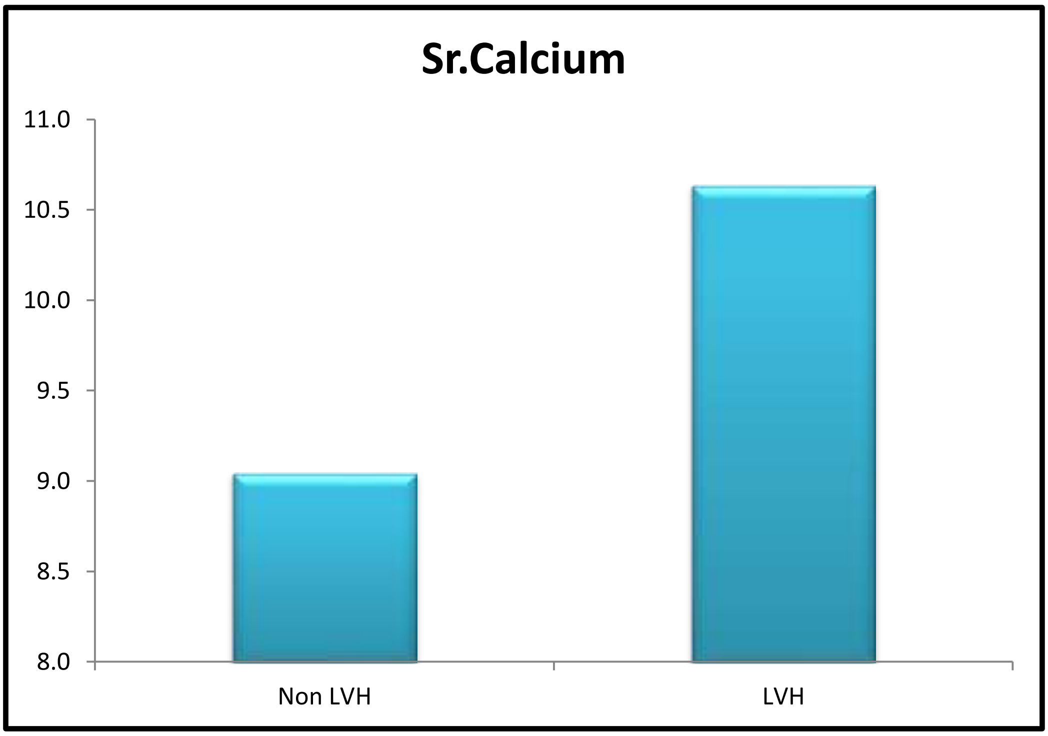
<u>Mean, standard deviation of variables in both LVH & non LVH Group:</u>

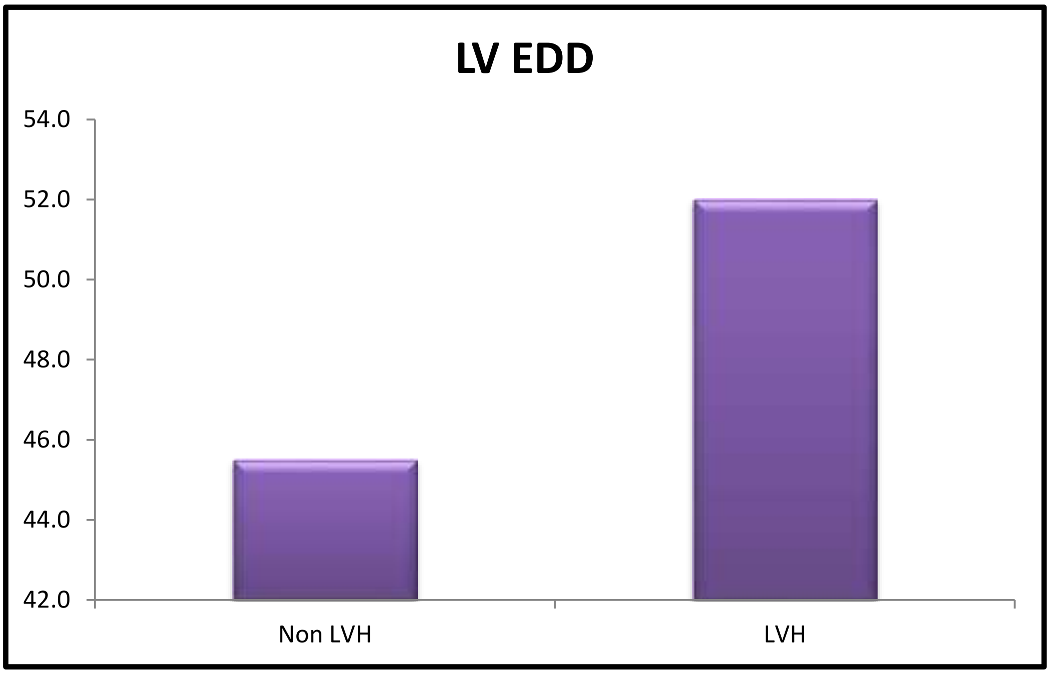
The mean age group in non LVH group people is 52.62 but it is 56.16 years in LVH group people. Gender does not make any significance in LVH prevalence. Serum calcium level is normal in non LVH group and the mean value is 9.04mg/dl. This calcium is high in LVH group people. The mean serum calcium level in LVH group peopleis 10.63. The value above 10.2 is considered to abnormal. The mean of left ventricular end diastolic dimension, interventricular septal wall thickness, posterior wall thickness, and relative wall thickness in LVH group is 52.01, 13.09, 10.99, 0.4233 respectively.

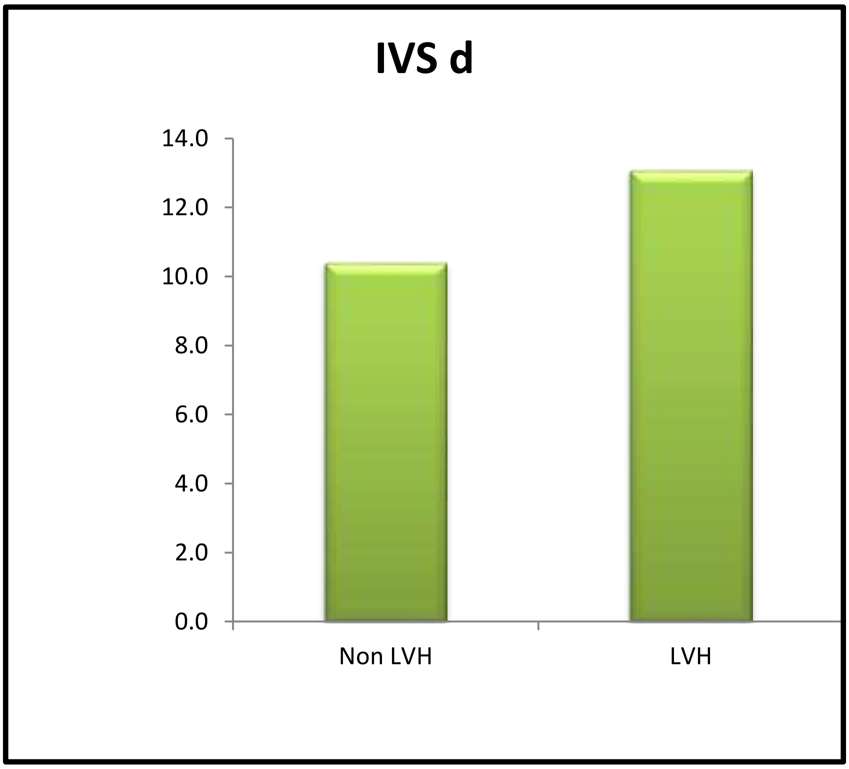
The mean left ventricular mass in LVH group is 229.51 but this low in non LVH group. After adjusting LV mass with body surface area the mean LV mass index in LVH group is 177.38. The mean cholesterol, triglycerides and LDL cholesterol in LVH group is 212.70, 159.47, 112.46 respectively.

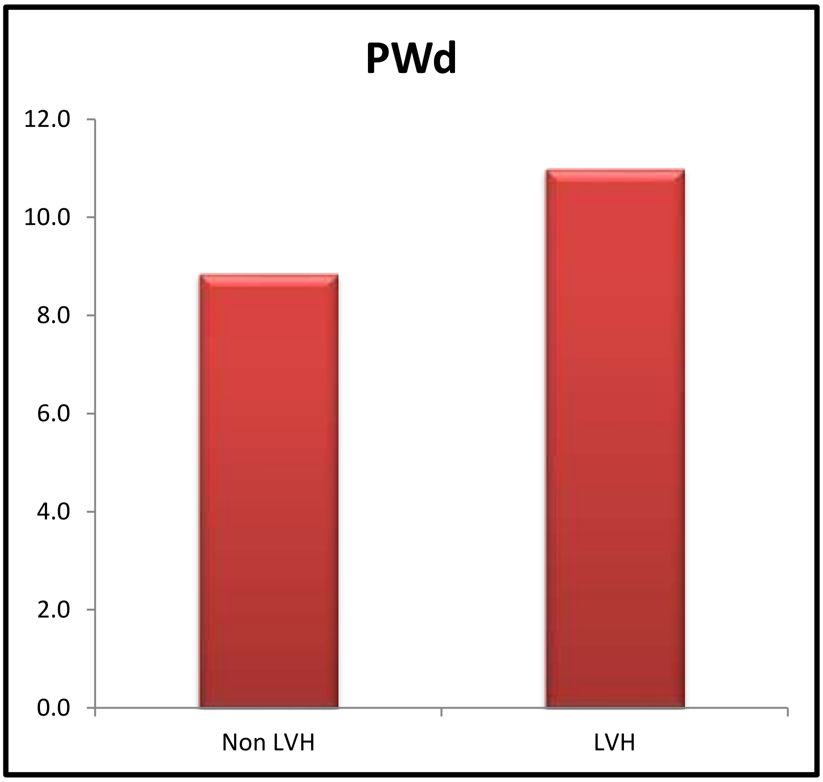
Groups		N	Mean	Std. Deviation	Std. Error Mean
AGE	Non LVH	102	52.62	5.794	.574
	LVH	104	56.16	6.889	.676
Sr.Calcium	Non LVH	102	9.0435	.08905	.00882
	LVH	104	10.6365	.27591	.02706
LV EDD	Non LVH	102	45.51	2.362	.234
	LVH	104	52.01	3.823	.375
IVS d	Non LVH	102	10.40	.761	.075
	LVH	104	13.09	1.359	.133
PWd	Non LVH	102	8.85	.604	.060
	LVH	104	10.99	1.186	.116
RWT	Non LVH	102	.3899	.02616	.00259
	LVH	104	.4233	.04514	.00443
LVMASS	Non LVH	102	148.23	20.414	2.021
	LVH	104	229.51	61.256	6.007
LVMI	Non LVH	102	90.60	12.638	1.251
	LVH	104	177.38	61.697	6.050
CHOLESTEROL	Non LVH	102	182.31	30.854	3.055
	LVH	104	212.70	36.546	3.584
TGL	Non LVH	102	131.96	31.825	3.151
	LVH	104	159.47	28.298	2.775
LDL	Non LVH	102	97.85	21.520	2.131
	LVH	104	112.46	18.140	1.779

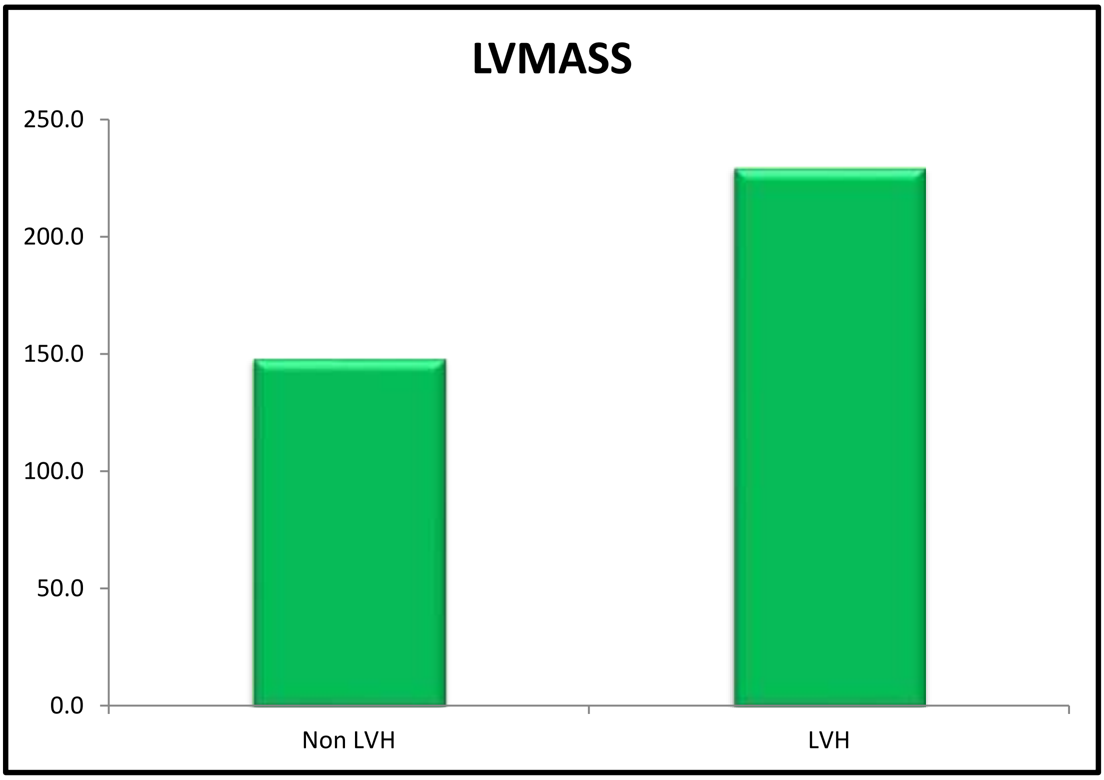

AGE
56
52
48
44
40
Non LVH
LVH

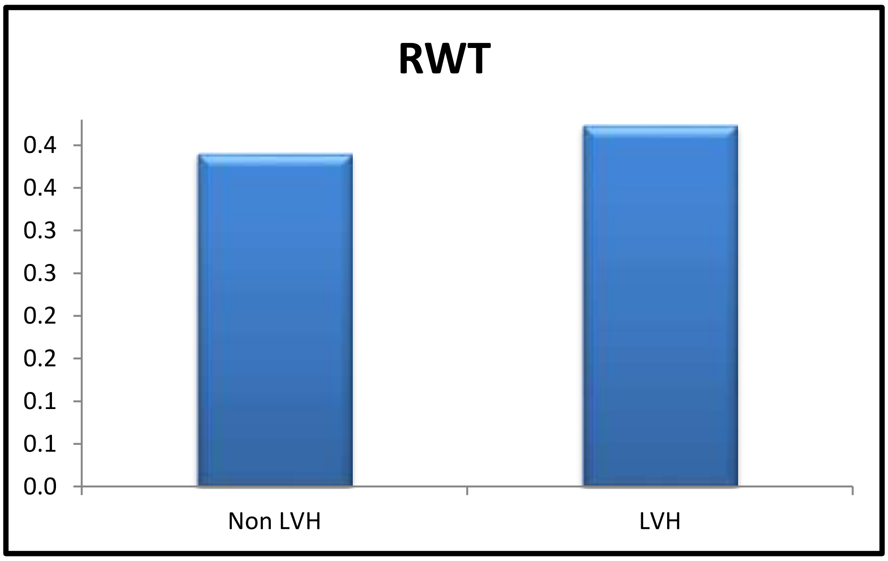

Sr.Calcium
11.0
10.5
10.0
9.5
9.0
8.5
8.0
Non LVH
LVH

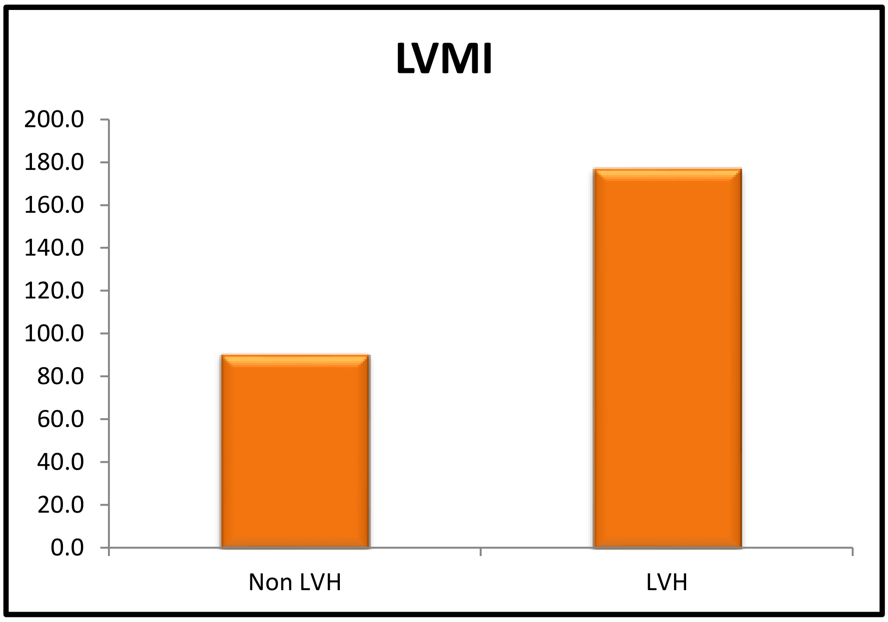

LV EDD
54.0
52.0
50.0
48.0
46.0
44.0
42.0
Non LVH
LVH


IVS d
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
Non LVH
LVH

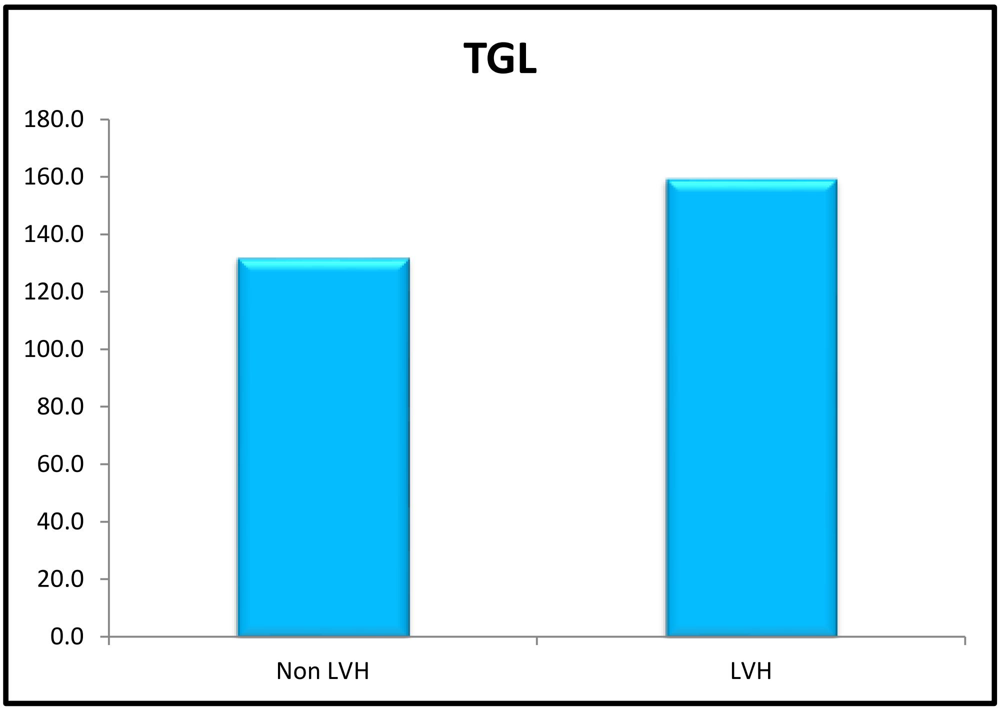

PWd
12.0
10.0
8.0
6.0
4.0
2.0
0.0
Non LVH
LVH

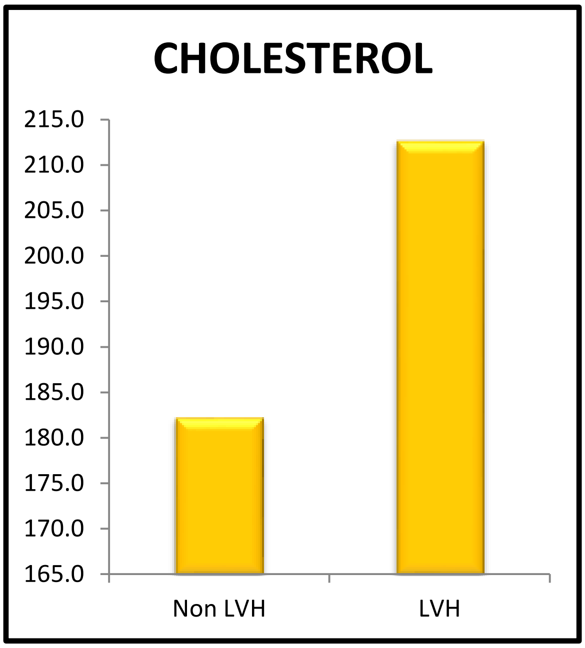

LVMASS
250.0
200.0
150.0
100.0
50.0
0.0
Non LVH
LVH

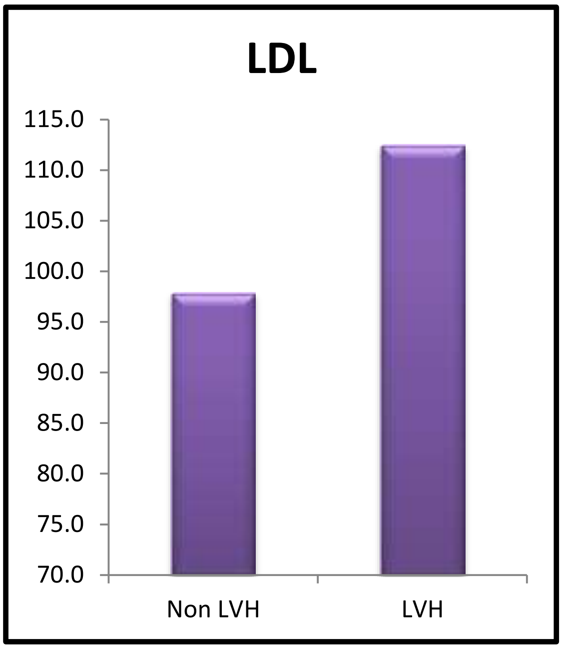




LVH is diagnosed as if LVMI > 115 in men and LVMI > 95 in women. If relative wall thickness and left ventricular mass index is normal that LV geometry is called as normal. Increased relative wall thickness and normal left ventricular mass index called concentric remodeling. Eccentric hypertrophy is defined as increased relative wall thickness and increased left ventricular mass index.


TGL
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0.0
Non LVH
LVH


CHOLESTEROL
215.0
210.0
205.0
200.0
195.0
190.0
185.0
180.0
175.0
170.0
165.0
Non LVH
LVH



<u>T test - to asses the significance of variables</u> :

In this study t test is used to assess the significance of variables towards the development of left ventricular remodeling. The p value is significant if it is <0.01. The serum calcium level p value is significant (p<0.005) in LVH group. It indicates the strong association of serum calcium for the development of left ventricular remodeling. Age also has significant p value in LVH group. Serum calcium levels are increasing in age advances. Serum cholesterol, LDL cholesterol, triglycerides also has a significant p value in LVH group population. But the gender makes any significance. The left ventricular end diastolic dimension, septal wall thickness, posterior wall thickness also have significant p value. This is the obvious one because the determinant of ventricular dimension is by above three parameters. The relative wall thickness is also significant in LVH group. But it does not make any change in left ventricular mass. It tells about the type of ventricular hypertrophy whether is it concentric or eccentric.

		Levene's Test for Equality of Variances		t-test for Equality of Means					
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference
									Lower
AGE	Equal variances assumed	6.585	.011	-3.994	204	.000	-3.546	.888	##
	Equal variances not assumed			-4.001	199.379	.0005	-3.546	.886	##
Sr.Calcium	Equal variances assumed	146.603	.000	-55.540	204	.000	-1.59301	.02868	##
	Equal variances not assumed			-55.982	124.608	.0005	-1.59301	.02846	##
LVMASS	Equal variances assumed	44.423	.000	-12.726	204	.000	-81.284	6.387	##
	Equal variances not assumed			-12.826	126.000	.0005	-81.284	6.338	##

LVMI	Equal variances assumed	94.892	.000	-13.922	204	.000	-86.787	6.234	##
	Equal variances not assumed			-14.048	111.794	.0005	-86.787	6.178	##
CHOLESTEROL	Equal variances assumed	3.338	.069	-6.443	204	.0005	-30.388	4.717	##
	Equal variances not assumed			-6.453	199.601	.000	-30.388	4.709	##
TGL	Equal variances assumed	.675	.412	-6.559	204	.0005	-27.510	4.194	##
	Equal variances not assumed			-6.552	200.279	.000	-27.510	4.199	##
LDL	Equal variances assumed	4.482	.035	-5.272	204	.000	-14.609	2.771	##
	Equal variances not assumed			-5.263	197.002	.0005	-14.609	2.776	##

Correlations[a] in LVH Groups

		Sr.Calcium	LV EDD	IVS d	PWd	RWT	LVMASS	LVMI	CHOLESTEROL	TGL	LDL
AGE	Pearson Correlation	-.087	.063	.021	.049	-.006	.146	-.064	-.139	-.118	-.118
	Sig. (2-tailed)	.377	.525	.830	.622	.953	.140	.517	.160	.232	.233
	N	104	104	104	104	104	104	104	104	104	104
Sr.Calcium	Pearson Correlation	1	.022	-.068	.022	.016	-.159	.143	.138	.012	.084
	Sig. (2-tailed)		.826	.492	.826	.872	.106	.147	.164	.906	.394
	N		104	104	104	104	104	104	104	104	104
LV EDD	Pearson Correlation		1	.267**	.373**	-.318**	.495**	.654**	.062	-.147	-.101
	Sig. (2-tailed)			.006	.000	.001	.000	.000	.530	.138	.307
	N			104	104	104	104	104	104	104	104
IVS d	Pearson Correlation			1	.470**	.313**	.520**	.456**	.157	-.143	.003
	Sig. (2-tailed)				.000	.001	.000	.000	.112	.148	.978
	N				104	104	104	104	104	104	104
PWd	Pearson Correlation				1	.758**	.593**	.454**	.402**	.178	.249*
	Sig. (2-tailed)					.000	.000	.000	.000	.071	.011
	N					104	104	104	104	104	104
RWT	Pearson Correlation					1	.264**	.009	.360**	.273**	.314**
	Sig. (2-tailed)						.007	.929	.000	.005	.001
	N						104	104	104	104	104

LVMASS	Pearson Correlation						1	-.001	-.023	-.171	-.062
	Sig. (2-tailed)							.992	.816	.082	.532
	N							104	104	104	104
LVMI	Pearson Correlation							1	.347**	.071	.128
	Sig. (2-tailed)								.000	.472	.196
	N								104	104	104
CHOLESTEROL	Pearson Correlation								1	.547**	.640**
	Sig. (2-tailed)									.000	.000
	N									104	104
TGL	Pearson Correlation									1	.668**
	Sig. (2-tailed)										.000
	N										104

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
a. Groups = LVH

Correlations[a] in Non LVH Groups

		Sr.Calcium	LV EDD	IVS d	PWd	RWT	LVMASS	LVMI	CHOLESTEROL	TGL	LDL
AGE	Pearson Correlation	.063	.077	.049	.055	.012	.105	.107	-.028	-.049	-.025
	Sig. (2-tailed)	.530	.444	.627	.586	.909	.291	.286	.779	.624	.806
	N	102	102	102	102	102	102	102	102	102	102
Sr.Calcium	Pearson Correlation	1	.009	.118	.135	.103	.070	.071	.064	.140	.152
	Sig. (2-tailed)		.926	.239	.176	.305	.484	.477	.523	.162	.128
	N		102	102	102	102	102	102	102	102	102
LV EDD	Pearson Correlation		1	.281**	.310**	-.450**	.824**	.824**	.019	.019	-.061
	Sig. (2-tailed)			.004	.002	.000	.000	.000	.850	.847	.542
	N			102	102	102	102	102	102	102	102
IVS d	Pearson Correlation			1	.669**	.460**	.717**	.717**	.174	.204*	.207*
	Sig. (2-tailed)				.000	.000	.000	.000	.080	.040	.037
	N				102	102	102	102	102	102	102
PWd	Pearson Correlation				1	.670**	.707**	.706**	-.018	-.012	-.046
	Sig. (2-tailed)					.000	.000	.000	.860	.903	.647
	N					102	102	102	102	102	102
RWT	Pearson Correlation					1	.078	.077	-.005	-.004	.033
	Sig. (2-tailed)						.437	.441	.957	.968	.740
	N						102	102	102	102	102
LVMASS	Pearson Correlation						1	1.000**	.055	.059	.024
	Sig. (2-tailed)							.000	.585	.553	.815
	N							102	102	102	102
LVMI	Pearson Correlation							1	.054	.062	.024
	Sig. (2-tailed)								.589	.539	.807
	N								102	102	102

CHOLESTEROL	Pearson Correlation								1	.628**	.814**
	Sig. (2-tailed)									.000	.000
	N									102	102
TGL	Pearson Correlation									1	.743**
	Sig. (2-tailed)										.000
	N										102

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

a. Groups = Non LVH

Discussion

Discussion

It is now clear that impaired calcium hemostasis is the key factor for cardiac hypertrophy, arrhyhthmias and heart failure. Other than direct calcium, dysfunction of calcium channels, proteins are also played a role in development of cardiac failure. Hypercalcemia causes hypertrophy in many ways. The most important mechanism is calcium calmodulin dependant calcineurin activation that leads translocation of NFAT protein into the nucleus. In myocardial cells mitochondria also regulates the calcium levels in dyadic space. The calcium overload condition leads to increased myocardial calcium uptake that leads to increased oxidative followed by mitochondrial dysfunction and death. Myocardial calcifications because of hypercalcemia impairs the ventricular relaxation and causes diastolic dysfunction. In our study calcium has high positive predictive value for the development of cardiac muscle hypertrophy. Increased serum calcium >10.2 is the margin for the development of cardiac hypertrophy. Calcium exerts its hypertrophic response through dyslipidemic effect by inhibiting cholesterol catabolism. But statistical analysis shows there is no direct correlation between LVH occurance and dyslipidemia. So it is cleared that LVH in diabetic patient is due to increased calcium levels. Increased calcium level has a positive correlation with LVH occurance. In our study wechecked the albumin adjusted serum calcium levels but we have excluded the conditions which causes hypoalbuminemia. This study only considered only 1 simple tests for LVH prediction. That is serum calcium which is highly cost effective. By our study results the main influencing factors for left ventricular hypertrophy is left ventricular end diastolic dimension, posterior wall thickness and inter ventricular septal thickness. But the increased calcium leads to thickness of all the walls. Hence produces left ventricular hypertrophy. Relative wall thickness classifies the type of hypertrophy whether it is concentric or eccentric. Along with this age is also a influencing the left ventricular hypertrophy. Initial detection is serum calcium can helpful to identify the risk of arrhythmias.

CONCLUSION OF THE STUDY

CONCLUSION

- Calcium is the important ion for cardiac and skeletal muscle contraction, maintain the blood coagulation and bone mineralization.
- Increased serum calcium will produce insulin resistance and vise versa.
- Serum calcium also increases the diabetic prevalence by interacting with GLUT 4 receptors.
- Normal calcium mandatory for excitation contraction coupling but high calcium adversely affects the ECC and produces ventricular dysfunction and through neurohormonal mechanism it produces cardiac muscle hypertrophy.
- According to this study increased serum calcium in diabetes has strong correlation with occurance of cardiac remodeling.
- Hence always check the serum calcium level in diabetic patient which will predict the development of LVH.
- Unnecessary calcium supplementation in diabetic patients WILL produces many adverse effects including left ventricle remodeling.

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BIBILIOGRAPHY

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ANNEXURE

MASTER CHART

MASTER CHART

GROUP 1 LVH

AGE	LVSD(cm)	LVDD(cm)	IVS(cm)	LVMASS	Sr.Calc	TGL	cholestrol	LDL
45/f	4.4	5.9	1.4	377.6	10.38	197	204	143
49/M	4.1	5.8	1.4	367.47	10.47	189	211	145
68/F	5.1	6.1	1.5	398.29	10.56	190	231	152
56/M	4.8	6	1.5	407.42	10.41	192	231	154
62/M	5.1	6.1	1.5	398.29	10.43	201	211	154
68/M	4.9	5.9	1.5	377.6	10.45	209	231	156
45/M	4.1	6.1	1.4	378.74	10.46	212	223	156
54/M	4.2	6.1	1.5	398.29	10.76	213	224	156
56/F	4.9	6.1	1.5	398.29	10.78	198	221	156
55/m	4.2	6.1	1.5	398.29	10.83	190	212	157
61/f	4.8	6	1.5	407.42	10.89	197	218	144
56/f	4.3	5.9	1.5	377.6	10.87	196	219	156
53/m	4.3	6	1.5	407.42	10.85	189	210	168
65/m	4.9	6.1	1.5	398.29	10.81	190	231	167
69/f	4.9	6.1	1.5	398.29	10.78	196	234	165
49/f	4.5	6.1	1.4	378.74	10.76	190	213	162
51/m	4.9	5.8	1.4	367.47	10.52	192	219	173
53/f	4.9	6.1	1.4	378.74	10.64	193	224	169
57/m	4.9	6	1.5	407.42	10.63	208	229	171
57/f	4.8	6.1	1.5	398.29	10.73	201	228	176
68/m	4.9	6.1	1.5	398.29	10.71	203	227	159
46/m	4.7	5.9	1.4	377.6	10.68	198	229	171
49/f	4.1	5.8	1.4	367.47	10.61	187	220	154
49/f	4.4	5.9	1.4	377.6	10.38	197	204	143
53/m	4.1	5.8	1.4	367.47	10.47	189	211	145
57/f	5.1	6.1	1.5	398.29	10.56	190	231	152
51/f	4.8	6	1.5	407.42	10.41	192	231	154
49/f	5.1	6.1	1.5	398.29	10.43	201	211	154
48/m	4.9	5.9	1.5	377.6	10.45	209	231	156
46/m	4.1	6.1	1.4	378.74	10.46	212	223	156
49/m	4.2	6.1	1.5	398.29	10.76	213	224	156
49/f	4.9	6.1	1.5	398.29	10.78	198	221	156
53/m	4.2	6.1	1.5	398.29	10.83	190	212	157
58/m	4.8	6	1.5	407.42	10.89	197	218	144
51/f	4.3	5.9	1.5	377.6	10.87	196	219	156
43/f	4.3	6	1.5	407.42	10.85	189	210	168
59/m	4.9	6.1	1.5	398.29	10.81	190	231	167
56/f	4.9	6.1	1.5	398.29	10.78	196	234	165
45/m	4.5	6.1	1.4	378.74	10.76	190	213	162
49/f	4.9	5.8	1.4	367.47	10.52	192	219	173

47/m	4.9	6.1	1.4	378.74	10.64	193	224	169
54/m	4.9	6	1.5	407.42	10.63	208	229	171
49/f	4.8	6.1	1.5	398.29	10.73	201	228	176
55/m	4.9	6.1	1.5	398.29	10.71	203	227	159
49/f	4.7	5.9	1.4	377.6	10.68	198	229	171
51/m	4.1	5.8	1.4	367.47	10.61	187	220	154
49/f	4.5	6.1	1.4	378.74	10.76	190	213	162
53/m	4.9	5.8	1.4	367.47	10.52	192	219	173
51/f	4.9	6.1	1.4	378.74	10.64	193	224	169
52/f	4.9	6	1.5	407.42	10.63	208	229	171
49/f	4.8	6.1	1.5	398.29	10.73	201	228	176
56/m	4.9	6.1	1.5	398.29	10.71	203	227	159
48/m	4.7	5.9	1.4	377.6	10.68	198	229	171
49/m	4.1	5.8	1.4	367.47	10.61	187	220	154
49/f	4.4	5.9	1.4	377.6	10.38	197	204	143
43/m	4.1	5.8	1.4	367.47	10.47	189	211	145
49/f	5.1	6.1	1.5	398.29	10.56	190	231	152
42/m	4.8	6	1.5	407.42	10.41	192	231	154
41/m	5.1	6.1	1.5	398.29	10.43	201	211	154
49/f	4.9	5.9	1.5	377.6	10.45	209	231	156
53/m	4.1	6.1	1.4	378.74	10.46	212	223	156
56/m	4.2	6.1	1.5	398.29	10.76	213	224	156
49/f	4.9	6.1	1.5	398.29	10.78	198	221	156
44/m	4.2	6.1	1.5	398.29	10.83	190	212	157
45/f	4.8	6	1.5	407.42	10.89	197	218	144
51/m	4.3	5.9	1.5	377.6	10.87	196	219	156
50/f	4.3	6	1.5	407.42	10.85	189	210	168
49/f	4.9	6.1	1.5	398.29	10.81	190	231	167
43/f	4.9	6.1	1.5	398.29	10.78	196	234	165
49/f	4.5	6.1	1.4	378.74	10.76	190	213	162
59/m	4.7	5.9	1.4	377.6	10.68	198	229	171
48/m	4.1	5.8	1.4	367.47	10.61	187	220	154
48/m	4.5	6.1	1.4	378.74	10.76	190	213	162
56/f	4.9	5.8	1.4	367.47	10.52	192	219	173
59/m	4.9	6.1	1.4	378.74	10.64	193	224	169
62/f	4.9	6	1.5	407.42	10.63	208	229	171
49/f	4.8	6.1	1.5	398.29	10.73	201	228	176
50/f	4.9	6.1	1.5	398.29	10.71	203	227	159
49/f	4.7	5.9	1.4	377.6	10.68	198	229	171
54/f	4.1	5.8	1.4	367.47	10.61	187	220	154
56/m	4.4	5.9	1.4	377.6	10.38	197	204	143
49/f	4.1	5.8	1.4	367.47	10.47	189	211	145
48/m	5.1	6.1	1.5	398.29	10.56	190	231	152
45/f	4.8	6	1.5	407.42	10.41	192	231	154

49/f	5.1	6.1	1.5	398.29	10.43	201	211	154
43/m	4.9	5.9	1.5	377.6	10.45	209	231	156
40/f	4.1	6.1	1.4	378.74	10.46	212	223	156
59/m	4.2	6.1	1.5	398.29	10.76	213	224	156
63/f	4.2	6.1	1.5	398.29	10.83	190	212	157
62/m	4.8	6	1.5	407.42	10.89	197	218	144
40/m	4.3	5.9	1.5	377.6	10.87	196	219	156
56/m	4.3	6	1.5	407.42	10.85	189	210	168
59/m	4.9	6.1	1.5	398.29	10.81	190	231	167
65/f	4.9	6.1	1.5	398.29	10.78	196	234	165

Group 2 NON LVH								
AGE	**LVSD**	**LVDD**	**IVS**	**LVMASS**	**Sr.Calc**	**TGL**	**cholestrol**	**LDL**
52/m	2.5	4.3	1	155.8	8.91	109	156	74
50/m	2.8	4.3	0.9	157.39	8.9	111	154	78
49/m	2.8	4.4	1	165.57	9.21	132	176	82
53/m	2.6	4.4	1	165.57	9.13	114	178	87
51/f	2.5	4.5	0.9	156.83	9.17	132	167	90
52/m	2.6	4.3	1	155.8	9.02	131	154	73
51/f	2.6	4.5	0.9	156.82	9.03	109	159	87
51/m	2.5	4.4	1	165.57	9.12	114	169	79
51/m	2.8	4.4	0.9	118.58	9.21	119	160	83
49/m	2.6	4.3	0.9	157.39	9.03	117	151	93
53/m	2.6	4.3	1	155.8	8.98	116	159	89
54/f	2.8	4.4	1	165.57	8.93	116	162	92
51/m	2.6	4.3	1	155.8	8.9	119	153	71
51/m	2.6	4.3	0.9	114.17	9.12	110	159	98
52/f	2.7	4.3	0.9	157.39	9.14	121	163	87
54/m	2.5	4.3	1	138.31	9.03	132	163	92
51/f	2.7	4.3	1	155.8	8.96	34	172	76
49/m	2.5	4.3	1	155.8	8.98	121	167	79
51/m	2.6	4.4	1	165.57	9.08	107	162	83
49/m	2.6	4.5	1	142.28	9.05	121	153	92
52/f	2.6	4.3	1	155.8	9.05	119	172	82
53/f	2.6	4.5	0.9	156.82	8.95	139	168	88
51/m	2.8	4.3	0.9	157.39	9.08	126	170	92
50/f	2.8	4.4	0.9	118.58	9.21	119	160	83
49/f	2.6	4.3	0.9	157.39	9.03	117	151	93
54/f	2.6	4.3	1	155.8	8.98	116	159	89
56/m	2.8	4.4	1	165.57	8.93	116	162	92
49/f	2.6	4.3	1	155.8	8.9	119	153	71
48/m	2.6	4.3	0.9	114.17	9.12	110	159	98
45/f	2.7	4.3	0.9	157.39	9.14	121	163	87
49/f	2.5	4.3	1	138.31	9.03	132	163	92

43/m	2.7	4.3	1	155.8	8.96	34	172	76
40/f	2.5	4.3	1	155.8	8.98	121	167	79
59/m	2.6	4.4	1	165.57	9.08	107	162	83
63/f	2.6	4.5	1	142.28	9.05	121	153	92
62/m	2.6	4.3	1	155.8	9.05	119	172	82
40/m	2.6	4.5	0.9	156.82	8.95	139	168	88
56/m	2.8	4.3	0.9	157.39	9.08	126	170	92
59/m	2.5	4.3	1	155.8	8.91	109	156	74
65/f	2.8	4.3	0.9	157.39	8.9	111	154	78
53/m	2.8	4.4	1	165.57	9.21	132	176	82
56/m	2.6	4.4	1	165.57	9.13	114	178	87
49/f	2.5	4.5	0.9	156.83	9.17	132	167	90
44/m	2.6	4.3	1	155.8	9.02	131	154	73
45/f	2.6	4.5	0.9	156.82	9.03	109	159	87
51/m	2.5	4.4	1	165.57	9.12	114	169	79
50/f	2.7	4.3	0.9	157.39	9.14	121	163	87
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48/m	2.6	4.5	1	142.28	9.05	121	153	92
48/m	2.6	4.3	1	155.8	9.05	119	172	82
56/f	2.6	4.5	0.9	156.82	8.95	139	168	88
59/m	2.8	4.3	0.9	157.39	9.08	126	170	92
62/f	2.5	4.3	1	155.8	8.91	109	156	74
49/f	2.8	4.3	0.9	157.39	8.9	111	154	78
58/m	2.8	4.4	1	165.57	9.21	132	176	82
51/f	2.6	4.4	1	165.57	9.13	114	178	87
43/f	2.6	4.3	1	155.8	8.9	119	153	71
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49/f	2.7	4.3	1	155.8	8.96	34	172	76
47/m	2.5	4.3	1	155.8	8.98	121	167	79
54/m	2.6	4.4	1	165.57	9.08	107	162	83
49/f	2.6	4.5	1	142.28	9.05	121	153	92
55/m	2.6	4.3	1	155.8	9.05	119	172	82
49/f	2.6	4.5	0.9	156.82	8.95	139	168	88
51/m	2.8	4.3	0.9	157.39	9.08	126	170	92
49/f	2.8	4.4	0.9	118.58	9.21	119	160	83
53/m	2.6	4.3	0.9	157.39	9.03	117	151	93
51/f	2.6	4.3	1	155.8	9.02	131	154	73
52/f	2.6	4.5	0.9	156.82	9.03	109	159	87
49/f	2.5	4.4	1	165.57	9.12	114	169	79

56/m	2.8	4.4	0.9	118.58	9.21	119	160	83
45/f	2.6	4.3	0.9	157.39	9.03	117	151	93
49/M	2.6	4.3	1	155.8	8.98	116	159	89
68/F	2.8	4.4	1	165.57	8.93	116	162	92
56/M	2.6	4.3	1	155.8	8.9	119	153	71
62/M	2.6	4.3	0.9	114.17	9.12	110	159	98
68/M	2.7	4.3	0.9	157.39	9.14	121	163	87
45/M	2.5	4.3	1	138.31	9.03	132	163	92
54/M	2.7	4.3	1	155.8	8.96	34	172	76
56/F	2.5	4.3	1	155.8	8.98	121	167	79
55/m	2.6	4.4	1	165.57	9.08	107	162	83
61/f	2.8	4.3	0.9	157.39	8.9	111	154	78
56/f	2.8	4.4	1	165.57	9.21	132	176	82
53/m	2.6	4.4	1	165.57	9.13	114	178	87
65/m	2.5	4.5	0.9	156.83	9.17	132	167	90
69/f	2.6	4.3	1	155.8	9.02	131	154	73
49/f	2.6	4.5	0.9	156.82	9.03	109	159	87
51/m	2.5	4.4	1	165.57	9.12	114	169	79
53/f	2.7	4.3	0.9	157.39	9.14	121	163	87
57/m	2.5	4.3	1	138.31	9.03	132	163	92
57/f	2.7	4.3	1	155.8	8.96	34	172	76
45/M	2.5	4.3	1	155.8	8.98	121	167	79
54/M	2.6	4.4	1	165.57	9.08	107	162	83
56/F	2.6	4.5	1	142.28	9.05	121	153	92
61/f	2.6	4.3	1	155.8	9.05	119	172	82
56/f	2.6	4.5	0.9	156.82	8.95	139	168	88
53/m	2.8	4.3	0.9	157.39	9.08	126	170	92

PLAGIARISM REPORT

URKUND

Urkund Analysis Result

Analysed Document: plag.docx (D42619229)
Submitted: 10/16/2018 12:52:00 PM
Submitted By: dhinapraveen30@gmail.com
Significance: 5 %

Sources included in the report:

thesis assh.docx (D31192330)
https://cardiab.biomedcentral.com/articles/10.1186/s12933-015-0200-9

Instances where selected sources appear:

13

PROFORMA

- **Name:** **Age/sex:**
- **Address:** **IPNO/OP NO:**
- **DM – Yes/No** **HT- Yes/ No**
- **Diagnosis:**
- **BMI:**

QUESTIONNAIRE:

- **Kuppusamy Socio economic State:**
- **Family History of DM / hypertension**
- **Do you exercise regularly :**
- **Diet restriction :**
- **H/o hypothyroidism/ hyperparathyroidism**
- **H/O previous cardiac illness :**
- **h/o any mediaction in past and current:**
- **h/o alcoholism / smoking**

சுயஒப்புதல்படிவம்

- ஆய்வுசெய்யப்படும்தலைப்பு:நீரிழிவுநோயில்அதிககால்சியத்தால்இருதயத்தில்ஏற்படும்பாதிப்புகள்பற்றியஆய்வு.
- இடம்:பொதுமருத்துவத்துவதுரை
  அரசுகீழ்பாக்கம்மருத்துவகல்லூரிமருத்துவமனை சென்னை
- பங்குபெறுபவரின்பெயர் :
- பங்குபெறுபவரின்வயது : பங்குபெறுபவரின்எண் :

மேலே குறிப்பிட்டுள்ள மருத்துவஆய்வின் விவரங்கள்எனக்கு விளக்கப்பட்டது. நான இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்தகாரணத்தினாலோ எந்த சட்டசிக்கலுக்கும்

உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக்கொள்ளல்லாம் என்றும் அறிந்துகொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும்போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என்னுடைய மருத்துவஅறிக்கைகளை பார்ப்பதற்கு என்அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன் இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்கமாட்டேன்.

இந்த ஆய்வில் பங்கு கொள்ள ஒப்புக் கொள்கிறேன்.

. இந்த ஆய்வை மேற்கொள்ளும் மருத்துவ அணிக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

பங்கேற்பவரின்கையொப்பம்

ஆய்வாளரின்கையொப்பம்

- இடம் :
- தேதி :

INSTITUTIONAL ETHICS COMMITTEE
GOVT. KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No. 49/2018 Meeting held on 12.02.2018

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "***A STUDY OF HIGH SERUM CALCIUM LEVEL IN DIABETES MELLITUS AND ITS ASSOCIATION WITH LEFT VENTRICULAR REMODELLING***" submitted by Dr.M.Praveenkumar, Post Graduate in General Medicine, Govt. Kilpauk Medical College, Chennai-10.

The Proposal is **APPROVED.**

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

26.2.2018

DEAN
Govt. Kilpauk Medical College,
Chennai-10.

ME 1 Sec> Ethical Committee